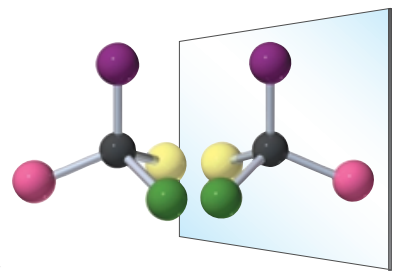
5 Stereochemistry

The Arrangement of Atoms in Space; The Stereochemistry of Addition Reactions



nonsuperimposable mirror images

Compounds that have the same molecular formula but are not identical are called **isomers**. Isomers fall into two main classes: *constitutional isomers* and *stereoisomers*. **Constitutional isomers** differ in the way their atoms are connected (Section 2.0). For example, ethanol and dimethyl ether are constitutional isomers because they have the same molecular formula, C_2H_6O, but the atoms in each compound are connected differently. The oxygen in ethanol is bonded to a carbon and to a hydrogen, whereas the oxygen in dimethyl ether is bonded to two carbons.

constitutional isomers

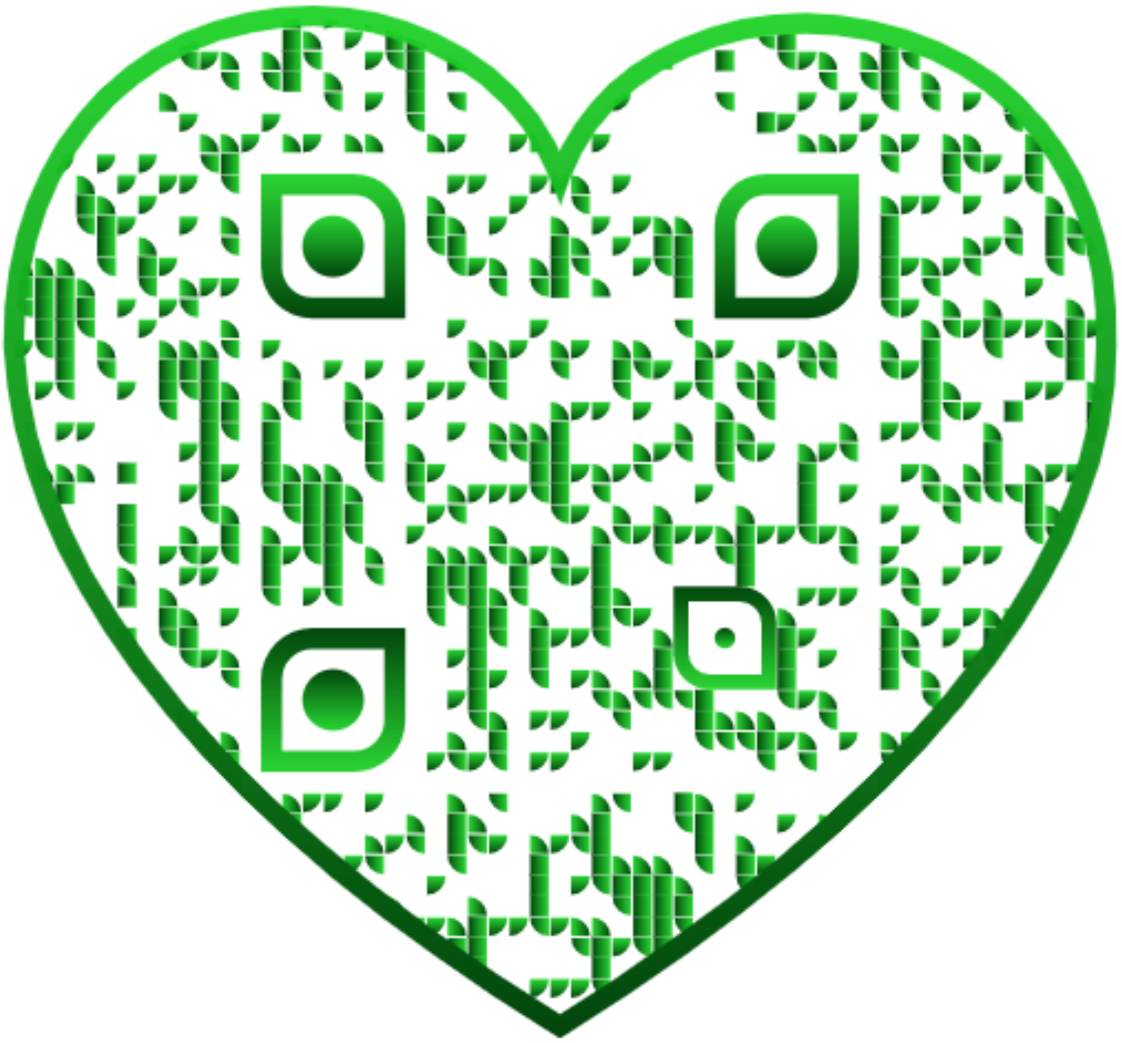
CH_3CH_2OH (ethanol) and CH_3OCH_3 (dimethyl ether)

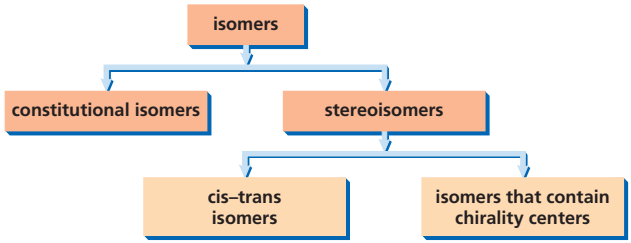
$CH_3CH_2CH_2CH_2Cl$ (1-chlorobutane) and $CH_3CH_2\underset{\displaystyle Cl}{\underset{|}{C}}HCH_3$ (2-chlorobutane)

$CH_3CH_2CH_2CH_2CH_3$ (pentane) and $CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2CH_3$ (isopentane)

$CH_3\overset{\displaystyle O}{\overset{\|}{C}}CH_3$ (acetone) and $CH_3CH_2\overset{\displaystyle O}{\overset{\|}{C}}H$ (propionaldehyde)

Unlike the atoms in constitutional isomers, the atoms in stereoisomers are connected in the same way. **Stereoisomers** (also called **configurational isomers**) differ in the way their atoms are arranged in space. Stereoisomers are different compounds that do not readily interconvert. Therefore, they can be separated. There are two kinds of stereoisomers: **cis–trans isomers** and isomers that contain chirality (ky-RAL-i-tee) centers.





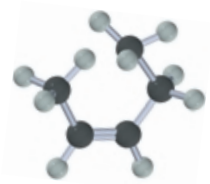
Movie: Isomerism

PROBLEM 1◆

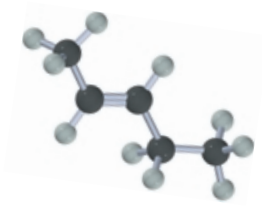
a. Draw three constitutional isomers with molecular formula C_3H_8O.
b. How many constitutional isomers can you draw for $C_4H_{10}O$?

5.1 Cis–Trans Isomers

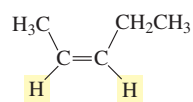
Cis–trans isomers (also called **geometric isomers**) result from restricted rotation (Section 3.4). Restricted rotation can be caused either by a double bond or by a cyclic structure. As a result of the restricted rotation about a carbon–carbon double bond, an alkene such as 2-pentene can exist as cis and trans isomers. The **cis isomer** has the hydrogens on the *same side* of the double bond, whereas the **trans isomer** has the hydrogens on *opposite sides* of the double bond.



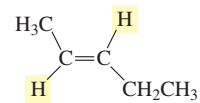
cis-2-pentene



trans-2-pentene



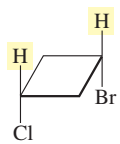
cis-2-pentene



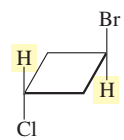
trans-2-pentene

Cyclic compounds can also have cis and trans isomers (Section 2.14). The cis isomer has the hydrogens on the same side of the ring, whereas the trans isomer has the hydrogens on opposite sides of the ring.

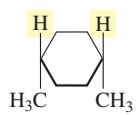
3-D Molecules: *cis*-2-Pentene; *trans*-2-Pentene



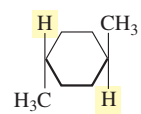
cis-1-bromo-3-chlorocyclobutane



trans-1-bromo-3-chlorocyclobutane



cis-1,4-dimethylcyclohexane



trans-1,4-dimethylcyclohexane

PROBLEM 2

Draw the cis and trans isomers for the following compounds:

a. 1-ethyl-3-methylcyclobutane
b. 2-methyl-3-heptene
c. 1-bromo-4-chlorocyclohexane
d. 1,3-dibromocyclobutane

5.2 Chirality

Why can't you put your right shoe on your left foot? Why can't you put your right glove on your left hand? It is because hands, feet, gloves, and shoes have right-handed and left-handed forms. An object with a right-handed and a left-handed form is said to be **chiral** (ky-ral). "Chiral" comes from the Greek word *cheir*, which means "hand." Notice that chirality is a property of an entire object.

A chiral object has a *nonsuperimposable mirror image*. In other words, its mirror image is not the same as itself. A hand is chiral because if you look at your left hand in a mirror, you do not see your left hand; you see your right hand (Figure 5.1). In contrast, a chair is not chiral—it looks the same in the mirror. Objects that are not chiral are said to be **achiral**. An achiral object has a *superimposable mirror image*. Some other achiral objects would be a table, a fork, and a glass.

PROBLEM 3◆

a. Name five capital letters that are chiral. b. Name five capital letters that are achiral.

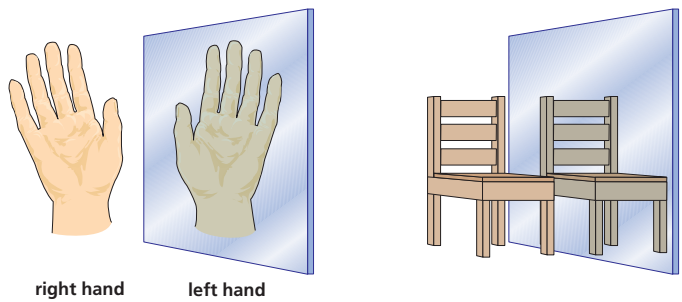


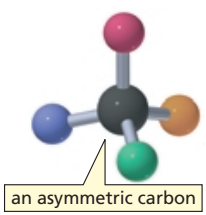
Figure 5.1 ▶
Using a mirror to test for chirality. A chiral object is not the same as its mirror image—they are nonsuperimposable. An achiral object is the same as its mirror image—they are superimposable.

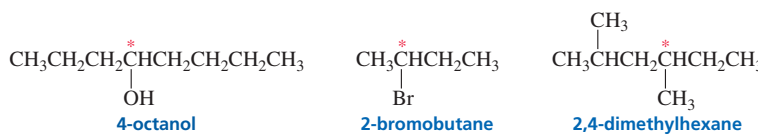
5.3 Asymmetric Carbons, Chirality Centers, and Stereocenters

Not only can objects be chiral, molecules can be chiral, too. The feature that most often is the cause of chirality in a molecule is an *asymmetric carbon*. (Other features that cause chirality are relatively uncommon and are beyond the scope of this book. You can, however, see one of these in Problem 88.)

An **asymmetric carbon** is a carbon atom that is bonded to four different groups. The asymmetric carbon in each of the following compounds is indicated by an asterisk. For example, the starred carbon in 4-octanol is an asymmetric carbon because it is bonded to four different groups (H, OH, $CH_2CH_2CH_3$, and $CH_2CH_2CH_2CH_3$). Notice that the difference in the groups bonded to the asymmetric carbon is not necessarily right next to the asymmetric carbon. For example, the propyl and butyl groups are different even though the point at which they differ is somewhat removed from the asymmetric carbon. The starred carbon in 2,4-dimethylhexane is an asymmetric carbon because it is bonded to four different groups—methyl, ethyl, isobutyl, and hydrogen.

A molecule with one asymmetric carbon is chiral.





Notice that the only carbons that can be asymmetric carbons are sp^3 hybridized carbons; sp^2 and sp hybridized carbons cannot be asymmetric carbons because they cannot have four groups attached to them.

An asymmetric carbon is also known as a **chirality center**. We will see that atoms other than carbon, such as nitrogen and phosphorus, can be chirality centers—when they are bonded to four different atoms or groups (Section 5.17). In other words, an asymmetric carbon is just one kind of chirality center. A chirality center also belongs to a broader group known as *stereocenters*. Stereocenters will be defined in Section 5.5.

Tutorial:
Identification of asymmetric carbon atoms

PROBLEM 4◆

Which of the following compounds have asymmetric carbons?

a. $CH_3CH_2\underset{\displaystyle Cl}{\underset{|}{C}}HCH_3$

b. $CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_3$

c. $CH_3CH_2\underset{\displaystyle Br}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}CH_2CH_2CH_3$

d. CH_3CH_2OH

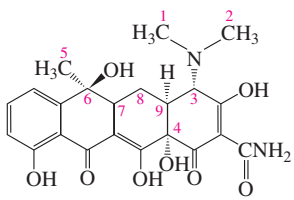
e. $CH_3CH_2\underset{\displaystyle Br}{\underset{|}{C}}HCH_2CH_3$

f. $CH_2{=}CH\underset{\displaystyle NH_2}{\underset{|}{C}}HCH_3$

PROBLEM 5 SOLVED

Tetracycline is called a broad-spectrum antibiotic because it is active against a wide variety of bacteria. How many asymmetric carbons does tetracycline have?

SOLUTION First, locate all the sp^3 hybridized carbons in tetracycline. (They are numbered in red.) Only sp^3 hybridized carbons can be asymmetric carbons, because an asymmetric carbon must have four different groups attached to it. Tetracycline has nine sp^3 hybridized carbons. Four of them (#1, #2, #5, and #8) are not asymmetric carbons because they are not bonded to four different groups. Tetracycline, therefore, has five asymmetric carbons.

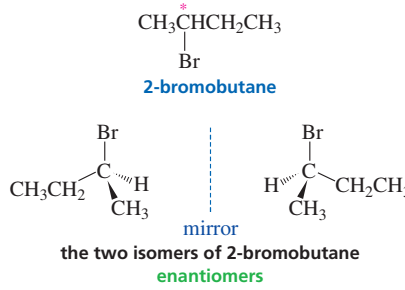


tetracycline

5.4 Isomers with One Asymmetric Carbon

A compound with one asymmetric carbon, such as 2-bromobutane, can exist as two different stereoisomers. The two isomers are analogous to a left and a right hand. Imagine a mirror between the two isomers; notice how they are mirror images of each other. The two stereoisomers are nonsuperimposable mirror images—they are different molecules.

Movie:
Nonsuperimposable mirror image

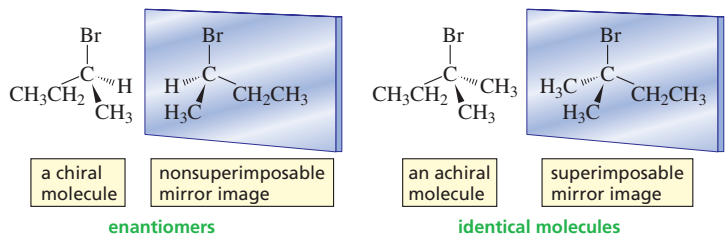


Take a break and convince yourself that the two 2-bromobutane isomers are not identical, by building ball-and-stick models using four different-colored balls to represent the four different groups bonded to the asymmetric carbon. Try to superimpose them.

Nonsuperimposable mirror-image molecules are called **enantiomers** (from the Greek *enantion*, which means "opposite"). The two stereoisomers of 2-bromobutane are enantiomers. A molecule that has a nonsuperimposable mirror image, like an object that has a nonsuperimposable mirror image, is chiral. Each of the enantiomers is chiral. A molecule that has a superimposable mirror image, like an object that has a superimposable mirror image, is achiral. To see that the achiral moleule is superimposable on its mirror image (i.e., they are identical molecules), mentally rotate the achiral molecule clockwise. Notice that chirality is a property of the entire molecule.

A chiral molecule has a nonsuperimposable mirror image.

An achiral molecule has a superimposable mirror image.



PROBLEM 6◆

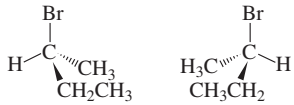
Which of the compounds in Problem 4 can exist as enantiomers?

5.5 Drawing Enantiomers

Chemists draw enantiomers using either *perspective formulas* or *Fischer projections*.

This book has been written in a way that allows you to use either perspective formulas or Fischer projections. Most chemists use perspective formulas. If you choose to use perspective formulas, you can ignore all the Fischer projections in the book.

Perspective formulas show two of the bonds to the asymmetric carbon in the plane of the paper, one bond as a solid wedge protruding out of the paper, and the fourth bond as a hatched wedge extending behind the paper. You can draw the first enantiomer by putting the four groups bonded to the asymmetric carbon in any order. Draw the second enantiomer by drawing the mirror image of the first enantiomer.



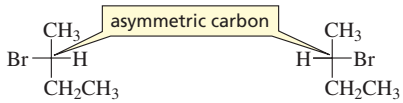
perspective formulas of the enantiomers of 2-bromobutane

The solid wedges represent bonds that point out of the plane of the paper toward the viewer.

The hatched wedges represent bonds that point back from the plane of the paper away from the viewer.

Make certain when you draw a perspective formula that the two bonds in the plane of the paper are adjacent to one another; neither the solid wedge nor the hatched wedge should be drawn between them.

A shortcut—called a **Fischer projection**—for showing the three-dimensional arrangement of groups bonded to an asymmetric carbon was devised in the late 1800s by Emil Fischer. A Fischer projecton represents an asymmetric carbon as the point of intersection of two perpendicular lines; horizontal lines represent the bonds that project out of the plane of the paper toward the viewer, and vertical lines represent the bonds that extend back from the plane of the paper away from the viewer. The carbon chain always is drawn vertically with C-1 at the top of the chain.



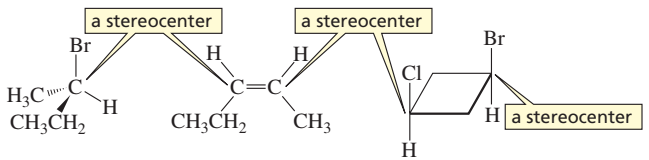
Fischer projections of the enantiomers of 2-bromobutane

In a Fischer projection horizontal lines project out of the plane of the paper toward the viewer and vertical lines extend back from the plane of the paper away from the viewer.

To draw enantiomers using a Fischer projection, draw the first enantiomer by arranging the four atoms or groups bonded to the asymmetric carbon in any order. Draw the second enantiomer by interchanging two of the atoms or groups. It does not matter which two you interchange. (Make models to convince yourself that this is true.) It is best to interchange the groups on the two horizontal bonds because the enantiomers then look like mirror images on paper.

Note that interchanging two atoms or groups gives you the enantiomer—whether you are drawing perspective formulas or Fischer projections. Interchanging two atoms or groups a second time, brings you back to the original molecule.

A **stereocenter** (or stereogenic center) is an atom at which the interchange of two groups produces a stereoisomer. Therefore, both *asymmetric carbons*—where the interchange of two groups produces an enantiomer and the carbons where the interchange of two groups converts a cis isomer to a trans isomer (or a *Z* isomer to an *E* isomer)—are stereocenters.



Emil Fischer (1852–1919) *was born in a village near Cologne, Germany. He became a chemist against the wishes of his father, a successful merchant, who wanted him to enter the family business. He was a professor of chemistry at the Universities of Erlangen, Würzburg, and Berlin. In 1902 he received the Nobel Prize in chemistry for his work on sugars. During World War I, he organized German chemical production. Two of his three sons died in that war.*

PROBLEM 7

Draw enantiomers for each of the following compounds using:

a. perspective formulas
b. Fischer projections

1. CH_3CHCH_2OH (Br)
2. $ClCH_2CH_2CHCH_2CH_3$ (CH_3)
3. $CH_3CHCHCH_3$ (CH_3, OH)

5.6 Naming Enantiomers: The *R*,*S* System of Nomenclature

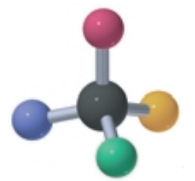
Robert Sidney Cahn (1899–1981), *was born in England and received an M.A. from Cambridge University and a doctorate in natural philosophy in France. He edited the* Journal of the Chemical Society *(London).*

Sir Christopher Ingold (1893–1970) *was born in Ilford, England, and was knighted by Queen Elizabeth II. He was a professor of chemistry at Leeds University (1924–1930) and at University College, London (1930–1970).*

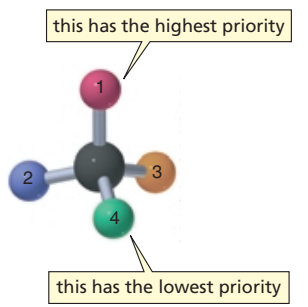
Vladimir Prelog (1906–1998) *was born in Sarajevo, Bosnia. In 1929 he received a Dr. Ing. degree from the Institute of Technology in Prague, Czechoslovakia. He taught at the University of Zagreb from 1935 until 1941, when he fled to Switzerland just ahead of the invading German army. He was a professor at the Swiss Federal Institute of Technology (ETH). For his work that contributed to an understanding of how living organisms carry out chemical reactions, he shared the 1975 Nobel Prize in chemistry with John Cornforth (page 231).*

We need a way to name the individual stereoisomers of a compound such as 2-bromobutane so that we know which stereoisomer we are talking about. In other words, we need a system of nomenclature that indicates the **configuration** (arrangement) of the atoms or groups about the asymmetric carbon. Chemists use the letters *R* and *S* to indicate the configuration about an asymmetric carbon. For any pair of enantiomers with one asymmetric carbon, one will have the ***R* configuration** and the other will have the ***S* configuration**. The *R*,*S* system was devised by Cahn, Ingold, and Prelog.

Let's first look at how we can determine the configuration of a compound if we have a three-dimensional model of the compound.

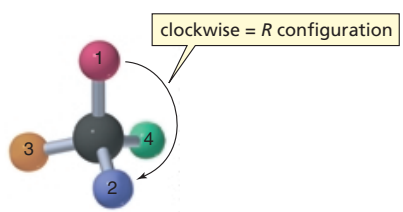


1. *Rank the groups (or atoms) bonded to the asymmetric carbon in order of priority*. The atomic numbers of the atoms directly attached to the asymmetric carbon determine the relative priorities. The higher the atomic number, the higher the priority. (This should remind you of the way relative priorities are determined for the *E*,*Z* system of nomenclature because the system of priorities was originally devised for the *R*,*S* system of nomenclature and was later borrowed for the *E*,*Z* system. You may want to revisit Section 3.5 to review how relative priorities are determined before you proceed with the *R*,*S* system.

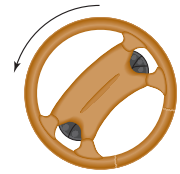


The molecule is oriented so the group with the lowest priority points away from the viewer. If an arrow drawn from the highest priority group to the next highest priority group points clockwise, the molecule has the *R* configuration.

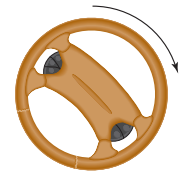
2. *Orient the molecule so that the group (or atom) with the lowest priority (4) is directed away from you. Then draw an imaginary arrow from the group (or atom) with the highest priority (1) to the group (or atom) with the next highest priority (2).* If the arrow points clockwise, the asymmetric carbon has the *R* configuration (*R* is for *rectus*, which is Latin for "right"). If the arrow points counterclockwise, the asymmetric carbon has the *S* configuration (*S* is for *sinister*, which is Latin for "left").



If you forget which is which, imagine driving a car and turning the steering wheel clockwise to make a right turn or counterclockwise to make a left turn.



left turn

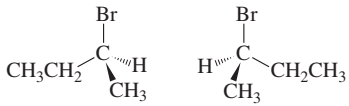


right turn

If you are able to easily visualize spatial relationships, the above two rules are all you need to determine whether the asymmetric carbon of a molecule written on a two-dimensional piece of paper has the *R* or the *S* configuration. Just mentally rotate the molecule so that the group (or atom) with the lowest priority (4) is directed away from you, then draw an imaginary arrow from the group (or atom) with the highest priority to the group (or atom) with the next highest priority.

If you have trouble visualizing spatial relationships and you don't have access to a model, the following will allow you to determine the configuration about an asymmetric carbon without having to mentally rotate the molecule.

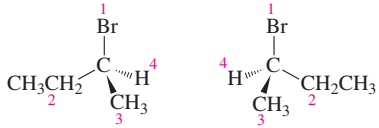
First, let's look at how you can determine the configuration of a compound drawn as a perspective formula. As an example, we will determine which of the enantiomers of 2-bromobutane has the *R* configuration and which has the *S* configuration.



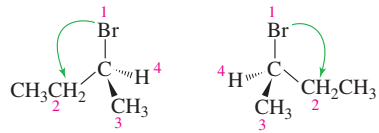
the enantiomers of 2-bromobutane

3-D Molecules: (*R*)-2-Bromobutane; (*S*)-2-Bromobutane

1. Rank the groups (or atoms) that are bonded to the asymmetric carbon in order of priority. In the following pair of enantiomers, bromine has the highest priority (1), the ethyl group has the second highest priority (2), the methyl group is next (3), and hydrogen has the lowest priority (4). (Revisit Section 3.5 if you don't understand how these priorities are assigned.)



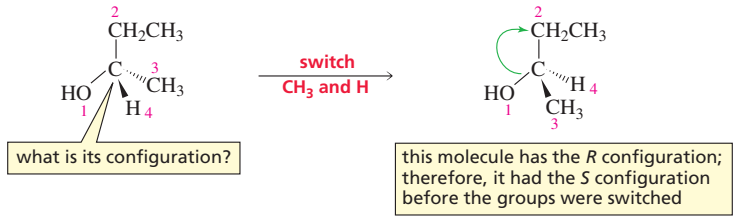
2. If the group (or atom) with the lowest priority is bonded by a hatched wedge, draw an arrow from the group (or atom) with the highest priority (1) to the group (or atom) with the second highest priority (2). If the arrow points clockwise, the compound has the *R* configuration, and if it points counterclockwise, the compound has the *S* configuration.



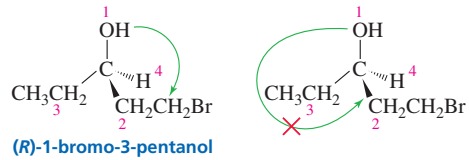
(*S*)-2-bromobutane (*R*)-2-bromobutane

Clockwise specifies *R* if the lowest priority substituent is on a hatched wedge.

3. If the group with the lowest priority (4) is NOT bonded by a hatched wedge, then switch two groups so group 4 is bonded by a hatched wedge. Then proceed as in step #2 (above): Draw an arrow from the group (or atom) with the highest priority (1) to the group (or atom) with the second highest priority (2). Because you have switched two groups, you are now determining the configuration of the enantiomer of the original molecule. So if the arrow points clockwise, the enantiomer (with the switched groups) has the *R* configuration, which means the original molecule has the *S* configuration. In contrast, if the arrow points counterclockwise, the enantiomer (with the switched groups) has the *S* configuration, which means the original molecule has the *R* configuration.


switch
CH3 and H
what is its configuration?
this molecule has the R configuration; therefore, it had the S configuration before the groups were switched

4. In drawing the arrow from group 1 to group 2, you can draw past the group with the lowest priority (4), but never draw past the group with the next lowest priority (3).

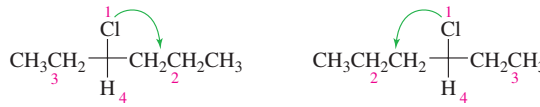


Now let's see how to determine the configuration of a compound drawn as a Fischer projection.

1. Rank the groups (or atoms) that are bonded to the asymmetric carbon in order of priority.

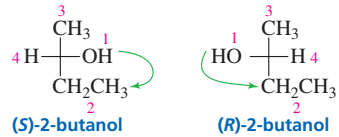
2. Draw an arrow from the group (or atom) with the highest priority (1) to the group (or atom) with the next highest priority (2). If the arrow points clockwise, the enantiomer has the *R* configuration; if it points counterclockwise, the enantiomer has the *S* configuration, *provided that the group with the lowest priority (4) is on a vertical bond.*

Clockwise specifies *R* if the lowest priority substituent is on a vertical bond.

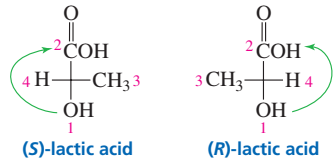


3. If the group (or atom) with the lowest priority is on a *horizontal* bond, the answer you get from the direction of the arrow will be the opposite of the correct answer. For example, if the arrow points clockwise, suggesting that the asymmetric carbon has the *R* configuration, it actually has the *S* configuration; if the arrow points counterclockwise, suggesting that the asymmetric carbon has the *S* configuration, it actually has the *R* configuration. In the following example, the group with the lowest priority is on a horizontal bond, so clockwise signifies the *S* configuration, not the *R* configuration.

Clockwise specifies *S* if the lowest priority substituent is on a horizontal bond.



4. In drawing the arrow from group 1 to group 2, you can draw past the group (or atom) with the lowest priority (4), but never draw past the group (or atom) with the next lowest priority (3).

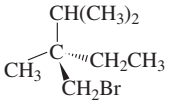


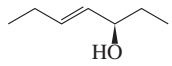
It is easy to tell whether two molecules are enantiomers (nonsuperimposable) or identical molecules (superimposable) if you have molecular models of the molecules—just see whether the models superimpose. If, however, you are working with structures on a two-dimensional piece of paper, the easiest way to determine whether two molecules are enantiomers or identical molecules is by determining their configurations. If one has the *R* configuration and the other has the *S* configuration, they are enantiomers. If they both have the *R* configuration or both have the *S* configuration, they are identical molecules.

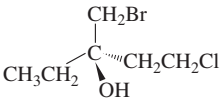
When comparing two Fischer projections to see if they are the same or different, never rotate one 90° or turn one over, because this is a quick way to get a wrong answer. A Fischer projection can be rotated 180° in the plane of the paper, but this is the only way to move it without risking an incorrect answer.

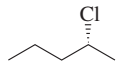
PROBLEM 8◆

Indicate whether each of the following structures has the *R* or the *S* configuration:

a. 

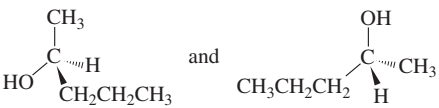
c. 

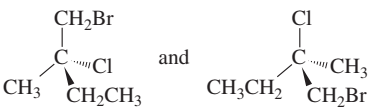
b. 

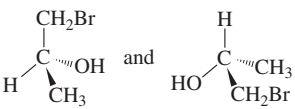
d. 

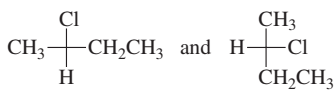
PROBLEM 9◆ SOLVED

Do the following structures represent identical molecules or a pair of enantiomers?

a. 

b. 

c. 

d. 

SOLUTION TO 9a The first structure shown in part (a) has the *S* configuration, and the second structure has the *R* configuration. Because they have opposite configurations, the structures represent a pair of enantiomers.

PROBLEM 10◆

Assign relative priorities to the following groups:

a. $-CH_2OH$ $-CH_3$ $-CH_2CH_2OH$ $-H$

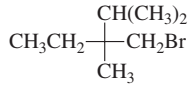
b. $-CH{=}O$ $-OH$ $-CH_3$ $-CH_2OH$

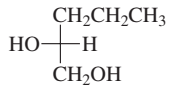
c. $-CH(CH_3)_2$ $-CH_2CH_2Br$ $-Cl$ $-CH_2CH_2CH_2Br$

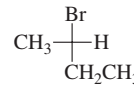
d. $-CH{=}CH_2$ $-CH_2CH_3$ $-CH_3$

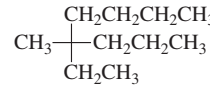
PROBLEM 11◆

Indicate whether each of the following structures has the *R* or the *S* configuration:

a. 

b. 

c. 

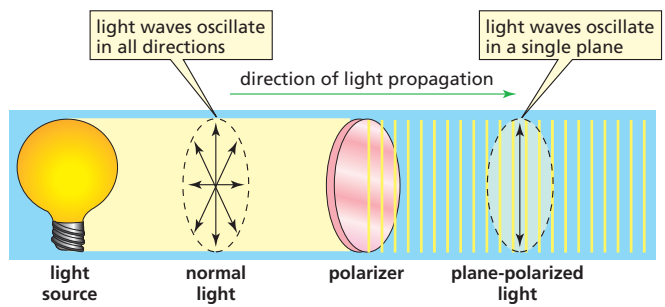
d. 

5.7 Optical Activity

Enantiomers share many of the same properties—they have the same boiling points, the same melting points, and the same solubilities. In fact, all the physical properties of enantiomers are the same except those that stem from how groups bonded to the asymmetric carbon are arranged in space. One of the properties that enantiomers do not share is the way they interact with polarized light.

Born in Scotland, **William Nicol (1768–1851)** *was a professor at the University of Edinburgh. He developed the first prism that produced plane-polarized light. He also developed methods to produce thin slices of materials for use in microscopic studies.*

What is polarized light? Normal light consists of electromagnetic waves that oscillate in all directions. **Plane-polarized light** (or simply polarized light), in contrast, oscillates only in a single plane passing through the path of propagation. Polarized light is produced by passing normal light through a polarizer such as a polarized lens or a Nicol prism.

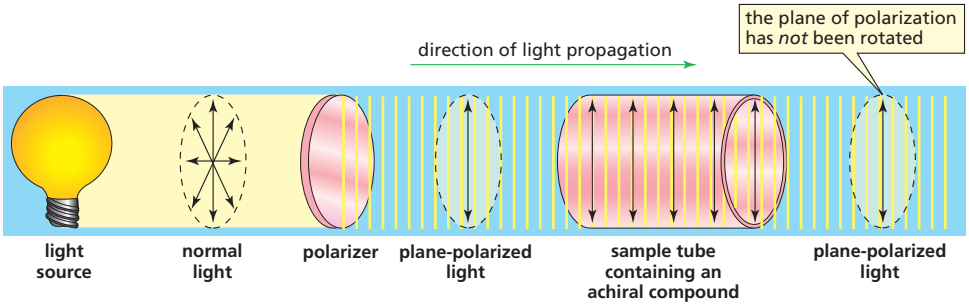


▲ When light is filtered through two polarized lenses at a 90° angle to one other, no light is transmitted through them.

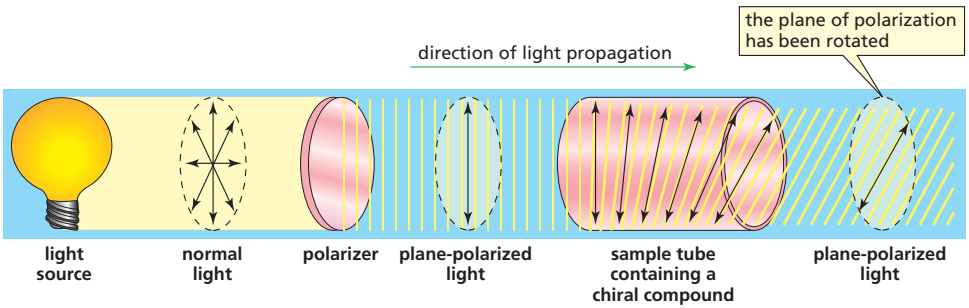
You experience the effect of a polarized lens with polarized sunglasses. Polarized sunglasses allow only light oscillating in a single plane to pass through them, so they block reflections (glare) more effectively than nonpolarized sunglasses.

In 1815, the physicist Jean-Baptiste Biot discovered that certain naturally occurring organic substances such as camphor and oil of turpentine are able to rotate the plane of polarization. He noted that some compounds rotated the plane of polarization clockwise and others counterclockwise, while some did not rotate the plane of polarization at all. He predicted that the ability to rotate the plane of polarization was attributable to some asymmetry in the molecules. Van't Hoff and Le Bel later determined that the molecular asymmetry was associated with compounds having one or more asymmetric carbons.

When polarized light passes through a solution of achiral molecules, the light emerges from the solution with its plane of polarization unchanged. *An achiral compound does not rotate the plane of polarization. It is optically inactive.*



However, when polarized light passes through a solution of a chiral compound, the light emerges with its plane of polarization changed. Thus, *a chiral compound rotates the plane of polarization*. A chiral compound will rotate the plane of polarization clockwise or counterclockwise. If one enantiomer rotates the plane of polarization clockwise, its mirror image will rotate the plane of polarization exactly the same amount counterclockwise.



A compound that rotates the plane of polarization is said to be **optically active**. In other words, chiral compounds are optically active and achiral compounds are **optically inactive**.

If an optically active compound rotates the plane of polarization clockwise, it is called **dextrorotatory**, indicated by (+). If an optically active compound rotates the plane of polarization counterclockwise, it is called **levorotatory**, indicated by (−). *Dextro* and *levo* are Latin prefixes for "to the right" and "to the left," respectively. Sometimes lowercase *d* and *l* are used instead of (+) and (−).

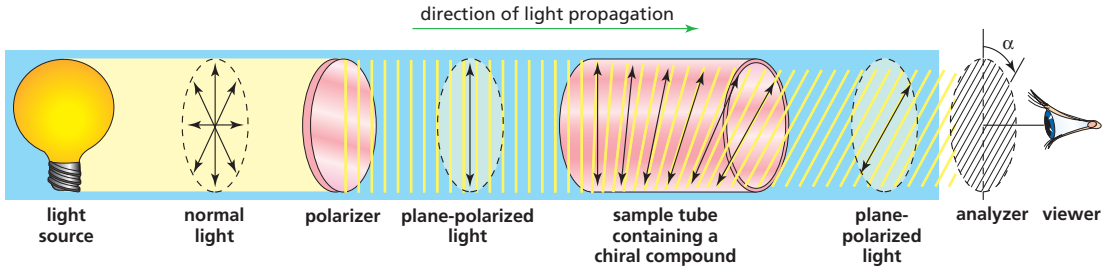
Do not confuse (+) and (−) with *R* and *S*. The (+) and (−) symbols indicate the direction in which an optically active compound rotates the plane of polarization, whereas *R* and *S* indicate the arrangement of the groups about an asymmetric carbon. Some compounds with the *R* configuration are (+) and some are (−).

The degree to which an optically active compound rotates the plane of polarization can be measured with an instrument called a **polarimeter** (Figure 5.2). Because the

Joseph Achille Le Bel (1847–1930), *a French chemist, inherited his family's fortune, which enabled him to establish his own laboratory. He and van't Hoff independently arrived at the reason for the optical activity of certain molecules. Although van't Hoff's explanation was more precise, both chemists are given credit for the work.*

Some molecules with the *R* configuration are (+), and some molecules with the *R* configuration are (−).

▼ Figure 5.2
Schematic of a polarimeter.



Movie:
Optical activity

amount of rotation will vary with the wavelength of the light used, the light source for a polarimeter must produce monochromatic (single wavelength) light. Most polarimeters use light from a sodium arc (called the sodium D-line; wavelength = 589 nm). In a polarimeter, monochromatic light passes through a polarizer and emerges as polarized light. The polarized light then passes through an empty sample tube (or one filled with an optically inactive solvent) and emerges with its plane of polarization unchanged. The light then passes through an analyzer. The analyzer is a second polarizer mounted on an eyepiece with a dial marked in degrees. When using a polarimeter, the analyzer is rotated until the user's eye sees total darkness. At this point the analyzer is at a right angle to the first polarizer, so no light passes through. This analyzer setting corresponds to zero rotation.

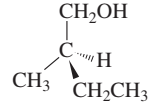
The sample to be measured is then placed in the sample tube. If the sample is optically active, it will rotate the plane of polarization. The analyzer will no longer block all the light, so light reaches the user's eye. The user then rotates the analyzer again until no light passes through. The degree to which the analyzer is rotated can be read from the dial and represents the difference between an optically inactive sample and the optically active sample. This is called the **observed rotation** (α); it is measured in degrees. The observed rotation depends on the number of optically active molecules the light encounters in the sample. This, in turn, depends on the concentration of the sample and the length of the sample tube. The observed rotation also depends on the temperature and the wavelength of the light source.

Each optically active compound has a characteristic specific rotation. The **specific rotation** is the number of degrees of rotation caused by a solution of 1.0 g of the compound per mL of solution in a sample tube 1.0 dm long at a specified temperature and wavelength. The specific rotation can be calculated from the observed rotation using the following formula:

$$[\alpha]_{\lambda}^{T} = \frac{\alpha}{l \times c}$$

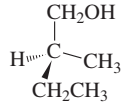
where $[\alpha]$ is the specific rotation; T is temperature in °C; λ is the wavelength of the incident light (when the sodium D-line is used, λ is indicated as D); α is the observed rotation; l is the length of the sample tube in decimeters; and c is the concentration of the sample in grams per milliliter of solution.

For example, one enantiomer of 2-methyl-1-butanol has been found to have a specific rotation of +5.75°. Because its mirror image rotates the plane of polarization the same amount but in the opposite direction, the specific rotation of the other enantiomer must be −5.75°.



(*R*)-2-methyl-1-butanol

$[\alpha]_{D}^{20\,°C} = +5.75°$



(*S*)-2-methyl-1-butanol

$[\alpha]_{D}^{20\,°C} = -5.75°$

PROBLEM 12◆

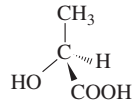
The observed rotation of 2.0 g of a compound in 50 mL of solution in a polarimeter tube 50-cm long is +13.4°. What is the specific rotation of the compound?

Knowing whether a chiral molecule has the *R* or the *S* configuration does not tell us the direction the compound rotates the plane of polarization, because some compounds with the *R* configuration rotate the plane to the right (+) and some rotate the plane to the left (−). We can tell by looking at the structure of a compound whether it has the *R* or the *S* configuration, but the only way we can tell whether a compound is

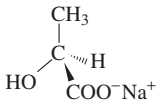
Jacobus Hendricus van't Hoff (1852–1911), *a Dutch chemist, was a professor of chemistry at the University of Amsterdam and later at the University of Berlin. He received the first Nobel Prize in chemistry (1901) for his work on solutions.*

Born in France, **Jean-Baptiste Biot (1774–1862)** *was imprisoned for taking part in a street riot during the French Revolution. He became a professor of mathematics at the University of Beauvais and later a professor of physics at the Collège de France. He was awarded the Legion of Honor by Louis XVIII.* *(Also see p. 212.)*

dextrorotatory (+) or levorotatory (−) is to put the compound in a polarimeter. For example, (*S*)-lactic acid and (*S*)-sodium lactate have the same configuration, but (*S*)-lactic acid is dextrorotatory whereas (*S*)-sodium lactate is levorotatory. When we know the direction an optically active compound rotates the plane of polarization, we can incorporate (+) or (−) into its name.



(*S*)-(+)-lactic acid



(*S*)-(−)-sodium lactate

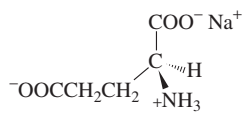
PROBLEM 13◆

a. Is (*R*)-lactic acid dextrorotatory or levorotatory?
b. Is (*R*)-sodium lactate dextrorotatory or levorotatory?

A mixture of equal amounts of two enantiomers—such as (*R*)-(−)-lactic acid and (*S*)-(+)-lactic acid—is called a **racemic mixture** or a **racemate**. Racemic mixtures do not rotate the plane of polarized light. They are optically inactive because for every molecule in a racemic mixture that rotates the plane of polarization in one direction, there is a mirror-image molecule that rotates the plane in the opposite direction. As a result, the light emerges from a racemic mixture with its plane of polarization unchanged. The symbol (±) is used to specify a racemic mixture. Thus, (±)-2-bromobutane indicates a mixture of (+)-2-bromobutane and an equal amount of (−)-2-bromobutane.

PROBLEM 14◆

(*S*)-(+)-Monosodium glutamate (MSG) is a flavor enhancer used in many foods. Some people have an allergic reaction to MSG (headache, chest pains, and an overall feeling of weakness). "Fast food" often contains substantial amounts of MSG, and it is widely used in Chinese food as well. MSG has a specific rotation of +24°.



(*S*)-(+)-monosodium glutamate

a. What is the specific rotation of (*R*)-(−)-monosodium glutamate?
b. What is the specific rotation of a racemic mixture of MSG?

5.8 Optical Purity and Enantiomeric Excess

Whether a particular sample consists of a single enantiomer or a mixture of enantiomers can be determined by its *observed specific rotation*. For example, an **enantiomerically pure** sample—meaning only one enantiomer is present—of (*S*)-(+)-2-bromobutane will have an *observed specific rotation* of +23.1° because the *specific rotation* of (*S*)-(+)-2-bromobutane is +23.1°. If, however, the sample of 2-bromobutane has an observed specific rotation of 0°, we will know that the compound is a racemic mixture. If the observed specific rotation is positive but less than +23.1°, we will know that we have a mixture of enantiomers and the mixture contains more of the enantiomer with the *S* configuration than the enantiomer with the *R* configuration. From the observed specific rotation, we can calculate the **optical purity (op)** of the mixture.

$$\text{optical purity} = \frac{\text{observed specific rotation}}{\text{specific rotation of the pure enantiomer}}$$

For example, if a sample of 2-bromobutane has an observed specific rotation of +9.2°, its optical purity is 0.40. In other words, it is 40% optically pure—40% of the mixture consists of an excess of a single enantiomer.

$$\text{optical purity} = \frac{+9.2^\circ}{+23.1^\circ} = 0.40 \text{ or } 40\%$$

Because the observed specific rotation is positive, we know that the solution contains excess (*S*)-(+)-2-bromobutane. The **enantiomeric excess (ee)** tells us how much excess (*S*)-(+)-2-bromobutane is in the mixture. As long as the compound is chemically pure, enantiomeric excess and optical purity will be the same.

$$\textbf{enantiomeric excess} = \frac{\textbf{excess of a single enantiomer}}{\textbf{entire mixture}} \times \textbf{100\%}$$

$$= \frac{\textbf{40\%}}{\textbf{100\%}} = \textbf{40\%}$$

If the mixture has a 40% enantiomeric excess, 40% of the mixture is excess *S* enantiomer and 60% is a racemic mixture. Half of the racemic mixture plus the amount of excess *S* enantiomer equals the amount of the *S* enantiomer present in the mixture. Thus, 70% of the mixture is the *S* enantiomer $(1/2 \times 60 + 40)$ and 30% is the *R* enantiomer.

PROBLEM 15◆

(+)-Mandelic acid has a specific rotation of +158°. What would be the observed specific rotation of each of the following mixtures?

a. 25% (−)-mandelic acid and 75% (+)-mandelic acid
b. 50% (−)-mandelic acid and 50% (+)-mandelic acid
c. 75% (−)-mandelic acid and 25% (+)-mandelic acid

PROBLEM 16◆

Naproxen, a nonsteroidal anti-inflammatory drug, is the active ingredient in Aleve. Naproxen has a specific rotation of +66° in chloroform. One commercial preparation results in a mixture that is 97% optically pure.

a. Does naproxen have the *R* or the *S* configurtion?
b. What percent of each enantiomer is obtained from the commercial preparation?

PROBLEM 17 SOLVED

A solution prepared by mixing 10 mL of a 0.10 M solution of the *R* enantiomer and 30 mL of a 0.10 M solution of the *S* enantiomer was found to have an observed specific rotation of +4.8°. What is the specific rotation of each of the enantiomers?

SOLUTION One (10.0 mL × 0.10 M) millimole (mmol) of the *R* enantiomer is mixed with 3 (30.0 mL × 0.10 M) mmol of the *S* enantiomer; 1 mmol of the *R* enantiomer plus 1 mmol of the *S* enantiomer will form 2 mmol of a racemic mixture. There will be 2 mmol of *S* enantiomer left over. Therefore, 2 mmol out of 4 mmol is excess *S* enantiomer $(2/4 = 0.50)$. The solution is 50% optically pure.

$$\text{optical purity} = 0.50 = \frac{\text{observed specific rotation}}{\text{specific rotation of the pure enantiomer}}$$

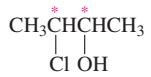
$$0.50 = \frac{+4.8^\circ}{x}$$

$$x = +9.6^\circ$$

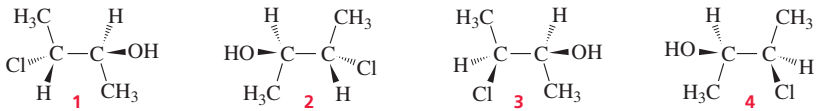
The *S* enantiomer has a specific rotation of +9.6°; the *R* enantiomer has a specific rotation of −9.6°.

5.9 Isomers with More than One Asymmetric Carbon

Many organic compounds have more than one asymmetric carbon. The more asymmetric carbons a compound has, the more stereoisomers are possible for the compound. If we know how many asymmetric carbons a compound has, we can calculate the maximum number of stereoisomers for that compound: *a compound can have a maximum of* 2^n *stereoisomers* (provided it doesn't have any other stereocenters), *where* n *equals the number of asymmetric carbons*. For example, 3-chloro-2-butanol has two asymmetric carbons. Therefore, it can have as many as four ($2^2 = 4$) stereoisomers. The four stereoisomers are shown both as perspective formulas and as Fischer projections.

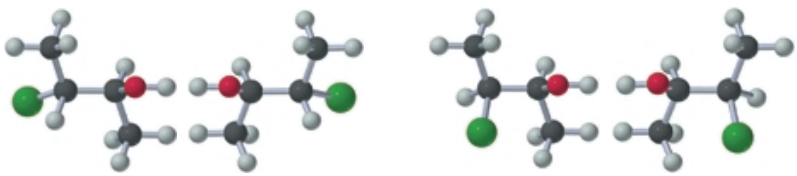


3-chloro-2-butanol

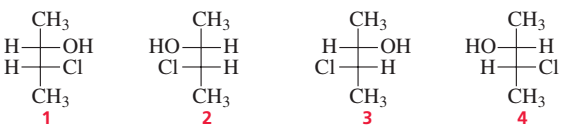


erythro enantiomers — threo enantiomers

perspective formulas of the stereoisomers of 3-chloro-2-butanol (staggered)



stereoisomers of 3-chloro-2-butanol



erythro enantiomers — threo enantiomers

Fisher projections of the stereoisomers of 3-chloro-2-butanol

3-D Molecules: (2*S*,3*S*)-3-Chloro-2-butanol; (2*S*,3*S*)-3-Chloro-2-butanol; (2*S*,3*S*)-3-Chloro-2-butanol; (2*R*,3*R*)-3-Chloro-2-butanol

The four stereoisomers of 3-chloro-2-butanol consist of two pairs of enantiomers. Stereoisomers **1** and **2** are nonsuperimposable mirror images. They, therefore, are enantiomers. Stereoisomers **3** and **4** are also enantiomers. Stereoisomers **1** and **3** are not identical, and they are not mirror images. Such stereoisomers are called diastereomers. **Diastereomers** are stereoisomers that are not enantiomers. Numbers **1** and **4**, **2** and **3**, and **2** and **4** are also diastereomers. (Cis–trans isomers are also considered to be diastereomers because they are stereoisomers that are not enantiomers.)

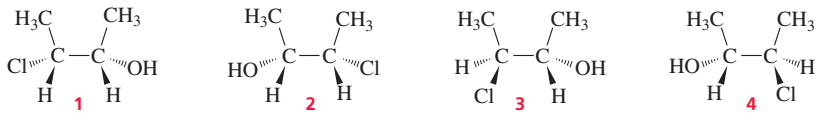
Diastereomers are stereoisomers that are not enantiomers.

Enantiomers have identical physical properties (except for the way they interact with polarized light) and identical chemical properties—they react at the same rate with a given achiral reagent. Diastereomers have different physical properties (different melting points, different boiling points, different solubilities, different specific rotations, and so on) and different chemical properties—they react with the same achiral reagent at different rates.

When Fischer projections are drawn for stereoisomers with two adjacent asymmetric carbons (such as those for 3-chloro-2-butanol), the enantiomers with similar

groups on the same side of the carbon chain are called the **erythro enantiomers** (Section 22.3). Those with similar groups on opposite sides are called the **threo enantiomers**. Therefore, **1** and **2** are the erythro enantiomers of 3-chloro-2-butanol (the hydrogens are on the same side), whereas **3** and **4** are the threo enantiomers. In each of the Fischer projections shown here, the horizontal bonds project out of the paper toward the viewer and the vertical bonds extend behind the paper away from the viewer. Groups can rotate freely about the carbon–carbon single bonds, but Fischer projections show the stereoisomers in their eclipsed conformations.

A Fischer projection does not show the three-dimensional structure of the molecule, and it represents the molecule in a relatively unstable eclipsed conformation. Most chemists, therefore, prefer to use perspective formulas because they show the molecule's three-dimensional structure in a stable, staggered conformation, so they provide a more accurate representation of structure. When perspective formulas are drawn to show the stereoisomers in their less stable eclipsed conformations, it can easily be seen—as the eclipsed Fischer projections show—that the erythro isomers have similar groups on the same side. We will use both prespective formulas and Fischer projections to depict the arrangement of groups bonded to an asymmetric carbon.

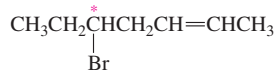


erythro enantiomers threo enantiomers

perspective formulas of the stereoisomers of 3-chloro-2-butanol (eclipsed)

PROBLEM 18

The following compound has only one asymmetric carbon. Why then does it have four stereoisomers?



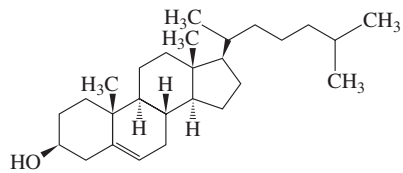
PROBLEM 19◆

a. Stereoisomers with two asymmetric carbons are called _____ if the configuration of both asymmetric carbons in one isomer is the opposite of the configuration of the asymmetric carbons in the other isomer.
b. Stereoisomers with two asymmetric carbons are called _____ if the configuration of both asymmetric carbons in one isomer is the same as the configuration of the asymmetric carbons in the other isomer.
c. Stereoisomers with two asymmetric carbons are called _____ if one of the asymmetric carbons has the same configuration in both isomers and the other asymmetric carbon has the opposite configuration in the two isomers.

PROBLEM 20◆

Tutorial: Identification of asymmetric carbons

a. How many asymmetric carbons does cholesterol have?
b. What is the maximum number of stereoisomers that cholesterol can have?
c. How many of these stereoisomers are found in nature?



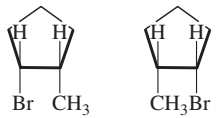
cholesterol

PROBLEM 21

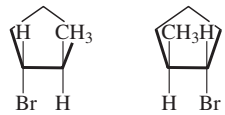
Draw the stereoisomers of 2,4-dichlorohexane. Indicate pairs of enantiomers and pairs of diastereomers.

3-D Molecules: (1*R*,2*S*)-1-Bromo-2-methylcyclopentane; (1*S*,2*R*)-1-Bromo-2-methylcyclopentane; (1*R*,2*R*)-1-Bromo-2-methylcyclopentane; (1*S*,2*S*)-1-Bromo-2-methylcyclopentane

1-Bromo-2-methylcyclopentane also has two asymmetric carbons and four stereoisomers. Because the compound is cyclic, the substituents can be in either the cis or the trans configuration. The cis isomer exists as a pair of enantiomers, and the trans isomer exists as a pair of enantiomers.

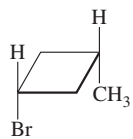


cis-1-bromo-2-methylcyclopentane

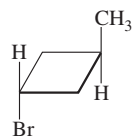


trans-1-bromo-2-methylcyclopentane

1-Bromo-3-methylcyclobutane does not have any asymmetric carbons. C-1 has a bromine and a hydrogen attached to it, but its other two groups (—$CH_2CH(CH_3)CH_2$—) are identical; C-3 has a methyl group and a hydrogen attached to it, but its other two groups (—$CH_2CH(Br)CH_2$—) are identical. Because the compound does not have a carbon with four different groups attached to it, it has only two stereoisomers, the cis isomer and the trans isomer. The cis and trans isomers do not have enantiomers.

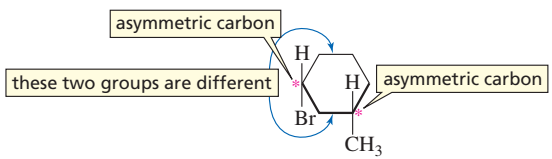


cis-1-bromo-3-methylcyclobutane

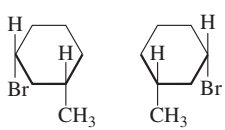


trans-1-bromo-3-methylcyclobutane

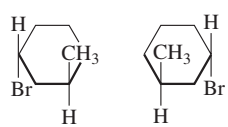
1-Bromo-3-methylcyclohexane has two asymmetric carbons. The carbon that is bonded to a hydrogen and a bromine is also bonded to two different carbon-containing groups (—$CH_2CH(CH_3)CH_2CH_2CH_2$— and —$CH_2CH_2CH_2CH(CH_3)CH_2$—), so it is an asymmetric carbon. The carbon that is bonded to a hydrogen and a methyl group is also bonded to two different carbon-containing groups, so it is also an asymmetric carbon.



Because the compound has two asymmetric carbons, it has four stereoisomers. Enantiomers can be drawn for the cis isomer, and enantiomers can be drawn for the trans isomer.

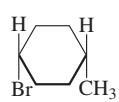


cis-1-bromo-3-methylcyclohexane

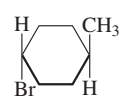


trans-1-bromo-3-methylcyclohexane

1-Bromo-4-methylcyclohexane has no asymmetric carbons. Therefore, the compound has only one cis isomer and one trans isomer.



cis-1-bromo-4-methylcyclohexane



trans-1-bromo-4-methylcyclohexane

PROBLEM 22

Draw all possible stereoisomers for each of the following compounds:

a. 2-chloro-3-hexanol
b. 2-bromo-4-chlorohexane
c. 2,3-dichloropentane
d. 1,3-dibromopentane

PROBLEM 23

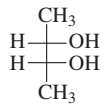
Draw the stereoisomers of 1-bromo-3-chlorocyclohexane.

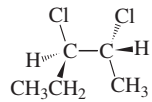
PROBLEM 24◆

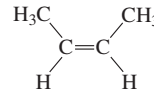
Of all the possible cyclooctanes that have one chloro substituent and one methyl substituent, which ones do not have any asymmetric carbons?

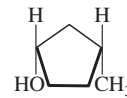
PROBLEM 25

Draw a diastereomer for each of the following.

a. 

b. 

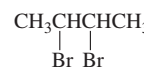
c. 

d. 

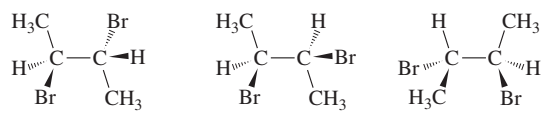
5.10 Meso Compounds

In the examples we have just seen, each compound with two asymmetric carbons has four stereoisomers. However, some compounds with two asymmetric carbons have only three stereoisomers. This is why we emphasized in Section 5.9 that the *maximum* number of stereoisomers a compound with *n* asymmetric carbons can have (provided it doesn't have any other stereocenters) is 2^n, instead of stating that a compound with *n* asymmetric carbons has 2^n stereoisomers.

An example of a compound with two asymmetric carbons that has only three stereoisomers is 2,3-dibromobutane.



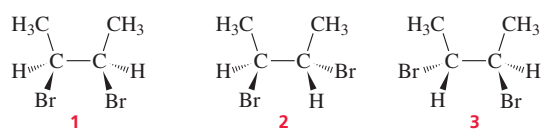
2,3-dibromobutane



1 2 3

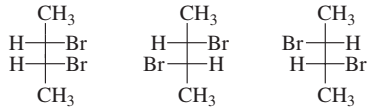
perspective formulas of the stereoisomers of 2,3-dibromobutane (staggered)

The "missing" isomer is the mirror image of **1** because **1** and its mirror image are the same molecule. This can be seen more clearly if you look either at the perspective formulas drawn in their eclisped conformations or at the Fischer projections.



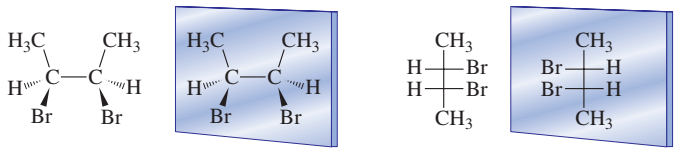
1 2 3

perspective formulas of the stereoisomers of 2,3-dibromobutane (eclipsed)



Fischer projections of the stereoisomers of 2,3-dibromobutane

It is obvious that **1** and its mirror image are identical when looking at the perspective formula in the eclipsed conformation. To convince yourself that the Fischer projection of **1** and its mirror image are identical, rotate the mirror image by 180°. *(Remember, you can move Fischer projections only by rotating them 180° in the plane of the paper.)*

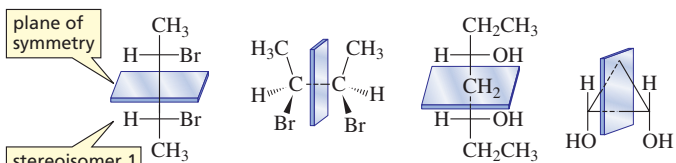


Stereoisomer **1** is called a *meso compound*. Even though a **meso** (mee-zo) **compound** has asymmetric carbons, it is an achiral molecule because it is superimposable on its mirror image. *Mesos* is the Greek word for "middle." A meso compound is achiral—when polarized light is passed through a solution of a meso compound, the plane of polarization is not rotated. A meso compound can be recognized by the fact that it has two or more asymmetric carbons and a plane of symmetry. *If a compound has a plane of symmetry, it will not be optically active even though it has asymmetric carbons*. A plane of symmetry cuts the molecule in half, and one-half is the mirror image of the other half. Stereoisomer **1** has a **plane of symmetry**, which means that it does *not* have a nonsuperimposable mirror image—it does not have an enantiomer.

A meso compound has two or more asymmetric carbons and a plane of symmetry.

A meso compound is achiral.

A chiral compound cannot have a plane of symmetry.

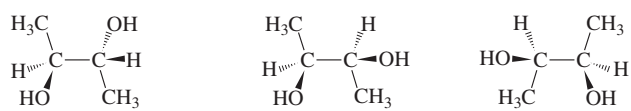


meso compounds

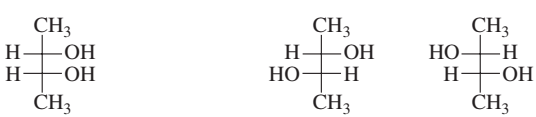
Movie:
Plane of symmetry

It is easy to recognize when a compound with two asymmetric carbons has a stereoisomer that is a meso compound—the four atoms or groups bonded to one asymmetric carbon are identical to the four atoms or groups bonded to the other asymmetric carbon. A compound with the same four atoms or groups bonded to two different asymmetric carbons will have three stereoisomers: One will be a meso compound, and the other two will be enantiomers.

If a compound with two asymmetric carbons has the same four groups bonded to each of the asymmetric carbons, one of its stereoisomers will be a meso compound.



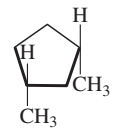
a meso compound **enantiomers**



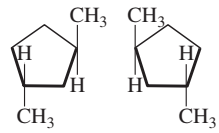
a meso compound **enantiomers**

3-D Molecules:
cis-1,3-Dimethylcyclopentane
and its mirror image

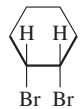
In the case of cyclic compounds, the cis isomer will be the meso compound and the trans isomer will exist as enantiomers.



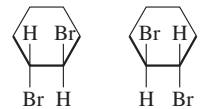
***cis*-1,3-dimethylcyclopentane**
a meso compound



***trans*-1,3-dimethylcyclopentane**
a pair of enantiomers

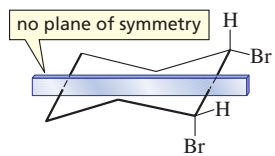


***cis*-1,2-dibromocyclohexane**
a meso compound

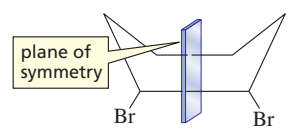


***trans*-1,2-dibromocyclohexane**
a pair of enantiomers

The preceding structure for *cis*-1,2-dibromocyclohexane suggests that the compound has a plane of symmetry. Cyclohexane, however, is not a planar hexagon—it exists preferentially in the chair conformation, and the chair conformer of *cis*-1,2-dibromocyclohexane does not have a plane of symmetry. Only the much less stable boat conformer of *cis*-1,2-dibromocyclohexane has a plane of symmetry. Then, is *cis*-1,2-dibromocyclohexane a meso compound? The answer is yes. As long as any one conformer of a compound has a plane of symmetry, the compound will be achiral, and an achiral compound with two asymmetric carbons is a meso compound.

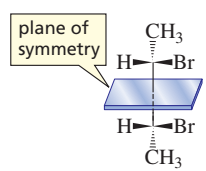


chair conformer

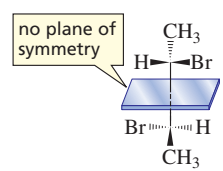


boat conformer

This holds for acyclic compounds as well. We have just seen that 2,3-dibromobutane is an achiral meso compound because it has a plane of symmetry. To see that it had a plane of symmetry, however, we had to look at a relatively unstable eclipsed conformer. The more stable staggered conformer does not have a plane of symmetry. 2,3-Dibromobutane is still a meso compound, however, because it has a conformer that has a plane of symmetry.



eclipsed conformer



staggered conformer

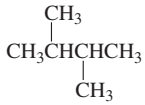
PROBLEM-SOLVING STRATEGY

Which of the following compounds has a stereoisomer that is a meso compound?

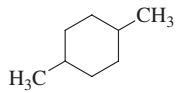
a. 2,3-dimethylbutane
b. 3,4-dimethylhexane
c. 2-bromo-3-methylpentane
d. 1,3-dimethylcyclohexane
e. 1,4-dimethylcyclohexane
f. 1,2-dimethylcyclohexane
g. 3,4-diethylhexane
h. 1-bromo-2-methylcyclohexane

Check each compound to see if it has the necessary requirements to have a stereoisomer that is a meso compound. That is, does it have two asymmetric carbons with the same four substituents attached to each of the asymmetric carbons?

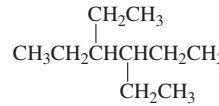
Compounds A, E, and G do *not* have a stereoisomer that is a meso compound because they don't have any asymmetric carbons.



A

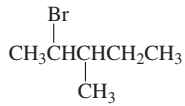


E

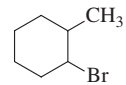


G

Compounds C and H each have two asymmetric carbons. They do *not* have a stereoisomer that is a meso compound because each of the asymmetric carbons is *not* bonded to the same four substituents.

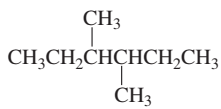


C

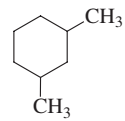


H

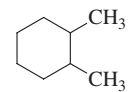
Compounds B, D, and F have a stereoisomer that is a meso compound—they have two asymmetric carbons and each asymmetric carbon is bonded to the same four atoms or groups.



B

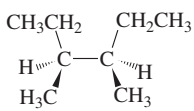


D

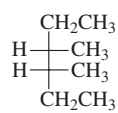


F

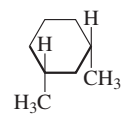
The isomer that is the meso compound is the one with a plane of symmetry when an acyclic compound is drawn in its eclipsed conformation (B), or when a cyclic compound is drawn with a planar ring (D and F).



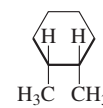
or



B



D



F

Now continue on to Problem 26.

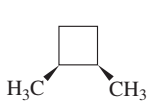
PROBLEM 26◆

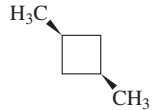
Which of the following compounds has a stereoisomer that is a meso compound?

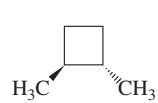
a. 2,4-dibromohexane
b. 2,4-dibromopentane
c. 2,4-dimethylpentane
d. 1,3-dichlorocyclohexane
e. 1,4-dichlorocyclohexane
f. 1,2-dichlorocyclobutane

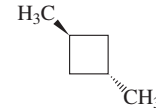
PROBLEM 27 SOLVED

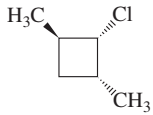
Which of the following are chiral?

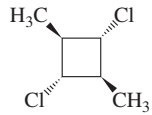


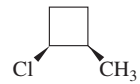


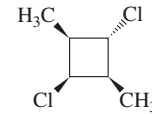




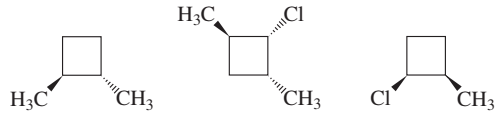








SOLUTION To be chiral, a molecule must not have plane of symmetry. Therefore, only the following compounds are chiral.



In the top row of compounds, only the third compound is chiral. The first, second, and fourth compounds each have a plane of symmetry. In the bottom row of compounds, the first and third compounds are chiral. The second and fourth compounds each have a plane of symmetry.

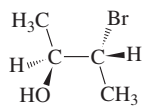
PROBLEM 28

Draw all the stereoisomers for each of the following compounds:

a. 1-bromo-2-methylbutane
b. 1-chloro-3-methylpentane
c. 2-methyl-1-propanol
d. 2-bromo-1-butanol
e. 3-chloro-3-methylpentane
f. 3-bromo-2-butanol
g. 3,4-dichlorohexane
h. 2,4-dichloropentane
i. 2,4-dichloroheptane
j. 1,2-dichlorocyclobutane
k. 1,3-dichlorocyclohexane
l. 1,4-dichlorocyclohexane
m. 1-bromo-2-chlorocyclobutane
n. 1-bromo-3-chlorocyclobutane

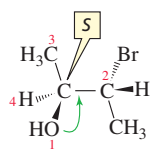
5.11 The *R,S* System of Nomenclature for Isomers with More than One Asymmetric Carbon

If a compound has more than one asymmetric carbon, the steps used to determine whether an asymmetric carbon has the *R* or the *S* configuration must be applied to each of the asymmetric carbons individually. As an example, let's name one of the stereoisomers of 3-bromo-2-butanol.

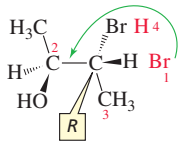


a stereoisomer of 3-bromo-2-butanol

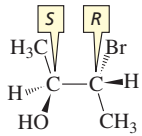
First, we will determine the configuration at C-2. The OH group has the highest priority, the C-3 carbon (the C attached to Br, C, H) has the next highest priority, CH_3 is next, and H has the lowest priority. Because the group with the lowest priority is bonded by a hatched wedge, we can immediately draw an arrow from the group with the highest priority to the group with the next highest priority. Because that arrow points counterclockwise, the configuration at C-2 is *S*.



Now we need to determine the configuration at C-3. Because the group with the lowest priority (H) is not bonded by a hatched wedge, we must put it there by temporarily switching two groups.

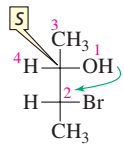


The arrow going from the highest priority group (Br) to the next highest priority group (the C attached to O, C, H) points counterclockwise, suggesting it has the *S* configuration. However, because we switched two groups before we drew the arrow, C-3 has the opposite configuration—it has the *R* configuration. Thus, the isomer is named (2*S*,3*R*)-3-bromo-2-butanol.

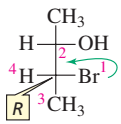


(2*S*,3*R*)-3-bromo-2-butanol

Fischer projections with two asymmetric carbons can be named in a similar manner. Just apply the steps to each asymmetric carbon that you learned for a Fischer projection with one asymmetric carbon. For C-2, the arrow from the group with the highest priority to the group with the next highest priority points clockwise, suggesting it has the *R* configuration. But because the group with the lowest priority is on a horizontal bond, we can conclude that C-2 has the *S* configuration (Section 5.6).

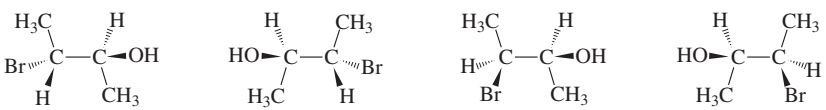


By repeating these steps for C-3, you will find that it has the *R* configuration. Thus, the isomer is named (2*S*,3*R*)-3-bromo-2-butanol.



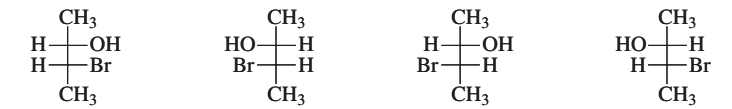
(2*S*,3*R*)-3-bromo-2-butanol

The four stereoisomers of 3-bromo-2-butanol are named as shown here. Take a few minutes to verify their names.



(2*S*,3*R*)-3-bromo-2-butanol | **(2*R*,3*S*)-3-bromo-2-butanol** | **(2*S*,3*S*)-3-bromo-2-butanol** | **(2*R*,3*R*)-3-bromo-2-butanol**

perspective formulas of the stereoisomers of 3-bromo-2-butanol



(2*S*,3*R*)-3-bromo-2-butanol | **(2*R*,3*S*)-3-bromo-2-butanol** | **(2*S*,3*S*)-3-bromo-2-butanol** | **(2*R*,3*R*)-3-bromo-2-butanol**

Fischer projections of the stereoisomers of 3-bromo-2-butanol

Notice that enantiomers have the opposite configuration at both asymmetric carbons, whereas diastereomers have the same configuration at one asymmetric carbon and the opposite configuration at the other.

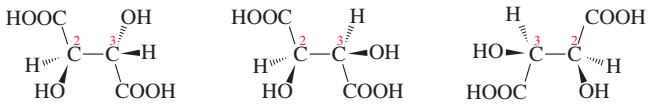
PROBLEM 29

Draw and name the four stereoisomers of 1,3-dichloro-2-butanol using:

a. perspective formulas

b. Fischer projections

Tartaric acid has three stereoisomers because each of its two asymmetric carbons has the same set of four substituents. The meso compound and the pair of enantiomers are named as shown.

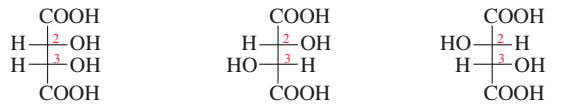


(2*R*,3*S*)-tartaric acid
a meso compound

(2*R*,3*R*)-tartaric acid
a pair of enantiomers

(2*S*,3*S*)-tartaric acid

perspective formulas of the stereoisomers of tartaric acid



(2*R*,3*S*)-tartaric acid
a meso compound

(2*R*,3*R*)-tartaric acid
a pair of enantiomers

(2*S*,3*S*)-tartaric acid

Fischer projections of the stereoisomers of tartaric acid

Tutorial:
Identification of stereoisomers with multiple asymmetric carbons

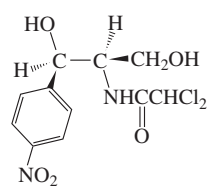
The physical properties of the three stereoisomers of tartaric acid are listed in Table 5.1. The meso compound and either one of the enantiomers are diastereomers. Notice that the physical properties of the enantiomers are the same, whereas the physical properties of the diastereomers are different. Also notice that the physical properties of the racemic mixture differ from the physical properties of the enantiomers.

Table 5.1 Physical Properties of the Stereoisomers of Tartaric Acid

	Melting point, °C	$[\alpha]_D^{25\,°C}$	Solubility, g/100 g H_2O at 15 °C
(2*R*,3*R*)-(+)-Tartaric acid	170	+11.98°	139
(2*S*,3*S*)-(−)-Tartaric acid	170	−11.98°	139
(2*R*,3*S*)-Tartaric acid	140	0°	125
(±)-Tartaric acid	206	0°	139

PROBLEM 30◆

Chloramphenicol is a broad-spectrum antibiotic that is particularly useful against typhoid fever. What is the configuration of each asymmetric carbon in chloramphenicol?



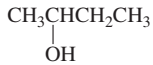
chloramphenicol

PROBLEM-SOLVING STRATEGY

Draw perspective formulas for the following compounds:

a. (*R*)-2-butanol b. (2*S*,3*R*)-3-chloro-2-pentanol

a. First draw the compound—ignoring the configuration at the asymmetric carbon—so you know what groups are bonded to the asymmetric carbon.

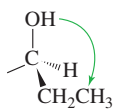


2-butanol

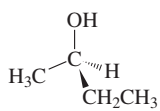
Draw the bonds about the asymmetric carbon.

Put the group with the lowest priority on the hatched wedge. Put the group with the highest priority on any remaining bond.

Because you have been asked to draw the *R* enantiomer, draw an arrow clockwise from the group with the highest priority to the next available bond and put the group with the next highest priority on that bond.

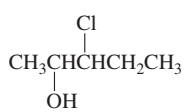


Put the remaining substituent on the last available bond.



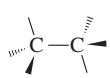
(*R*)-2-butanol

b. First draw the compound, ignoring the configuration at the asymmetric carbon.

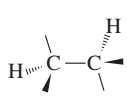


3-chloro-2-pentanol

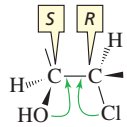
Draw the bonds about the asymmetric carbons.



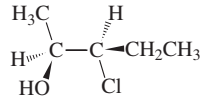
For each asymmetric carbon, put the group with the lowest priority on the hatched wedge.



For each asymmetric carbon, put the group with the highest priority on a bond such that an arrow points clockwise (if you want the *R* configuration) or counterclockwise (if you want the *S* configuration) to the group with the next highest priority.



Put the remaining substituents on the last available bonds.



(2*S*,3*R*)-3-chloro-2-pentanol

Now continue on to Problem 31.

PROBLEM 31

Draw perspective formulas for the following compounds:

a. (*S*)-3-chloro-1-pentanol

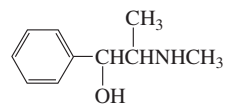
b. (2*R*,3*R*)-2,3-dibromopentane

c. (2*S*,3*R*)-3-methyl-2-pentanol

d. (*R*)-1,2-dibromobutane

PROBLEM 32◆

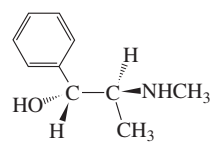
For many centuries, the Chinese have used extracts from a group of herbs known as ephedra to treat asthma. Chemists have been able to isolate a compound from these herbs, which they named ephedrine, a potent dilator of air passages in the lungs.



ephedrine

a. How many stereoisomers are possible for ephedrine?

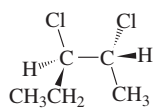
b. The stereoisomer shown here is the one that is pharmacologically active. What is the configuration of each of the asymmetric carbons?



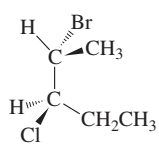
PROBLEM 33◆

Name the following compounds:

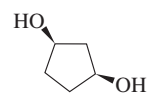
a.



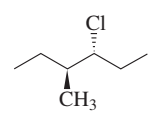
b.



c.

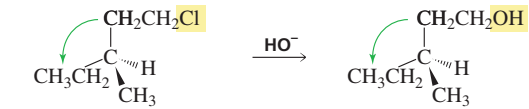


d.



5.12 Reactions of Compounds that Contain an Asymmetric Carbon

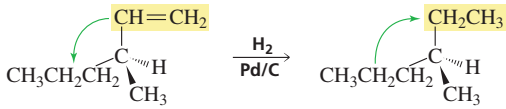
When a compound that contains an asymmetric carbon undergoes a reaction, what happens to the configuration of the asymmetric carbon depends on the reaction. If the reaction does not break any of the four bonds to the asymmetric carbon, then the relative positions of the groups bonded to the asymmetric carbon will not change. For example, when (*S*)-1-chloro-3-methylhexane reacts with hydroxide ion, OH substitutes for Cl. The reactant and the product have the same **relative configuration** because the reaction does not break any of the bonds to the asymmetric carbon.



(*S*)-1-chloro-3-methylhexane (*S*)-3-methyl-1-hexanol

If a reaction does not break a bond to the asymmetric carbon, the reactant and the product will have the same relative configurations.

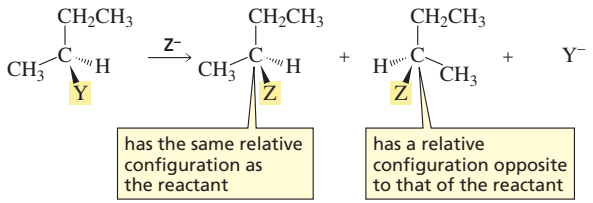
A word of warning: If the four groups bonded to the asymmetric carbon maintain their relative positions, it does not necessarily mean that an *S* reactant will always yield an *S* product as occurred in the preceding reaction. In the following example, the groups maintained their relative positions during the reaction. Therefore, the reactant and the product have the same *relative configurations*. However, the reactant has the *S* configuration, whereas the product has the *R* configuration. Although, the groups maintained their relative positions, their relative priorities—as defined by the Cahn–Ingold–Prelog rules—changed (Section 5.5). The change in priorities—not the change in positions of the groups—is what caused the *S* reactant to become an *R* product.



(*S*)-3-methylhexene (*R*)-3-methylhexane

The reactant and product in this example have the same relative configuration, but they have different **absolute configurations**—the reactant has the *S* configuration, whereas the product has the *R* configuration. The actual configuration is called the absolute configuration to indicate that the configuration is known in an absolute sense rather than in a relative sense. Knowing the *absolute configuration* of a compound means that you know whether it has the *R* or the *S* configuration. Knowing that two compounds have the same *relative configuration* means that they have the same relative positions of their substituents.

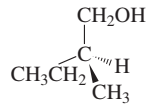
We have just seen that if the reaction does not break any of the bonds to the asymmetric carbon, the reactant and product will have the same relative configuration. In contrast, if the reaction *does break* a bond to the asymmetric carbon, the product can have the same relative configuration as the reactant or it can have the opposite relative configuration. Which of the products is actually formed depends on the mechanism of the reaction. Therefore, we cannot predict what the configuration of the product will be unless we know the mechanism of the reaction.



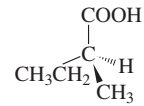
If a reaction does break a bond to the asymmetric carbon, you cannot predict the configuration of the product unless you know the mechanism of the reaction.

PROBLEM 34 SOLVED

(*S*)-(−)-2-Methyl-1-butanol can be converted to (+)-2-methylbutanoic acid without breaking any of the bonds to the asymmetric carbon. What is the configuration of (−)-2-methylbutanoic acid?



(*S*)-(−)-2-methyl-1-butanol

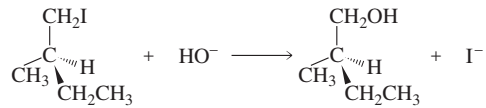


(+)-2-methylbutanoic acid

SOLUTION We know that (+)-2-methylbutanoic acid has the relative configuration shown because it was formed from (*S*)-(−)-2-methyl-1-butanol without breaking any bonds to the asymmetric carbon. Therefore, we know that (+)-2-methylbutanoic acid has the *S* configuration. We can conclude then that (−)-2-methylbutanoic acid has the *R* configuration.

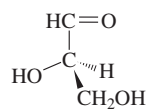
PROBLEM 35◆

The stereoisomer of 1-iodo-2-methylbutane with the *S* configuration rotates the plane of polarized light counterclockwise. The following reaction results in an alcohol that rotates the plane of polarized light clockwise. What is the configuration of (−)-2-methyl-1-butanol?

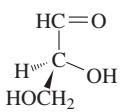


5.13 The Absolute Configuration of (+)-Glyceraldehyde

Glyceraldehyde has one chirality center and, therefore, has two stereoisomers. The absolute configuration of glyceraldehde was not known until 1951. Until then, chemists did not know whether (+)-glyceraldehyde had the *R* or the *S* configuration, although they had arbitrarily decided that it had the *R* configuration. They had a 50–50 chance of being correct.

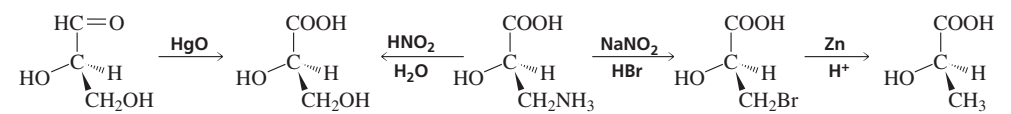


(*R*)-(+)-glyceraldehyde



(*S*)-(−)-glyceraldehyde

The configurations of many organic compounds were "determined" by synthesizing them from (+)- or (−)-glyceraldehyde or by converting them to (+)- or (−)-glyceraldehyde, always using reactions that did not break any of the bonds to the asymmetric carbon. For example, (−)-lactic could be related to (+)-glyceraldehyde through the following reactions. Thus the configuration of (−)-lactic was assumed to be that shown below. Because it was assumed that (+)-glyceraldehyde was the *R* enantiomer, the configurations assigned to these molecules were relative configurations, not absolute configurations. They were relative to (+)-glyceraldehyde, and were based on the *assumption* that (+)-glyceraldehyde had the *R* configuration.



(+)-glyceraldehyde — (−)-glyceric acid — (+)-isoserine — (−)-3-bromo-2-hydroxypropanoic acid — (−)-lactic acid

In 1951, the Dutch chemists J. M. Bijvoet, A. F. Peerdeman, and A. J. van Bommel, using X-ray crystallography and a new technique known as anomalous dispersion, determined that the sodium rubidium salt of (+)-tartaric acid had the *R*,*R* configuration. Because (+)-tartaric acid could be synthesized from (−)-glyceraldehyde, (−)-glyceraldehyde had to be the *S* enantiomer. The assumption, therefore, that (+)-glyceraldehyde had the *R* configuration was correct!

(–)-glyceraldehyde (+)-tartaric acid

The work of these chemists immediately provided absolute configurations for all those compounds whose relative configurations had been determined by relating them to (+)-glyceraldehyde. Thus, (−)-lactic acid has the configuration shown above. If (+)-glyceraldehyde had been the *S* enantiomer, (−)-lactic acid would have had the opposite configuration.

PROBLEM 36◆

What is the absolute configuration of the following?

a. (−)-glyceric acid
b. (+)-isoserine
c. (−)-glyceraldehyde
d. (+)-lactic acid

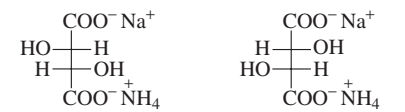
PROBLEM 37◆

Which of the following is true?

a. If two compounds have the same relative configuration, they will have the same absolute configuration.
b. If two compounds have the same relative configuration and you know the absolute configuration of either one of them, you can determine the absolute configuration of the other.
c. If two compounds have the same relative configuration, you can determine the absolute configuration of only one of them.
d. An *R* reactant always forms an *S* product.

5.14 Separating Enantiomers

Enantiomers cannot be separated by the usual separation techniques such as fractional distillation or crystallization because their identical boiling points and solubilities cause them to distill or crystallize simultaneously. Louis Pasteur was the first to separate a pair of enantiomers successfully. While working with crystals of sodium ammonium tartrate, he noted that the crystals were not identical—some of the crystals were "right-handed" and some were "left-handed." He painstakingly separated the two kinds of crystals with a pair of tweezers. He found that a solution of the right-handed crystals rotated the plane of polarized light clockwise, whereas a solution of the left-handed crystals rotated the plane of polarized light counterclockwise.



sodium ammonium tartrate left-handed crystals

sodium ammonium tartrate right-handed crystals

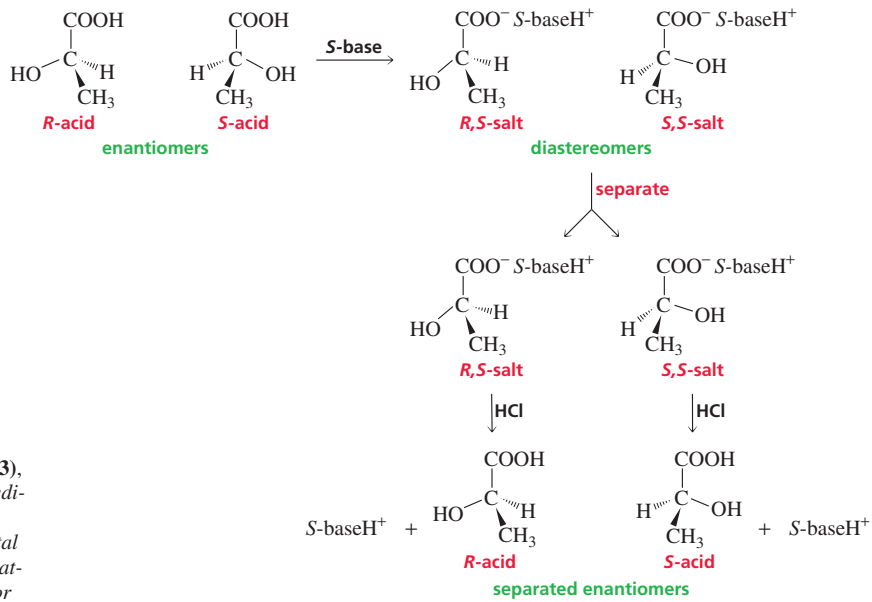
The French chemist and microbiologist **Louis Pasteur (1822–1895)** *was the first to demonstrate that microbes cause specific diseases. Asked by the French wine industry to find out why wine often went sour while aging, he showed that microorganisms cause grape juice to ferment, producing wine, and cause wine to slowly become sour. Gently heating the wine after fermentation, a process called pasteurization, kills the organisms so they cannot sour the wine.*

Pasteur was only 26 years old at the time and was unknown in scientific circles. He was concerned about the accuracy of his observations because a few years earlier, the well-known German organic chemist Eilhardt Mitscherlich had reported that crystals of the same salt were all identical. Pasteur immediately reported his findings to Jean-Baptiste Biot and repeated the experiment with Biot present. Biot was convinced that Pasteur had successfully separated the enantiomers of sodium ammonium tartrate. Pasteur's experiment also created a new chemical term. Tartaric acid is obtained from grapes, so it was also called racemic acid (*racemus* is Latin for "a bunch of grapes"). When Pasteur found that tartaric acid was actually a mixture of enantiomers, he called it a "racemic mixture." Separation of enantiomers is called the **resolution of a racemic mixture**.

Later, chemists recognized how lucky Pasteur had been. Sodium ammonium tartrate forms asymmetric crystals only under certain conditions—precisely the conditions that Pasteur had employed. Under other conditions, the symmetrical crystals that had fooled Mitscherlich are formed. But to quote Pasteur, "Chance favors the prepared mind."

Separating enantiomers by hand, as Pasteur did, is not a universally useful method to resolve a racemic mixture because few compounds form asymmetric crystals. A more commonly used method is to convert the enantiomers into diastereomers. Diastereomers can be separated because they have different physical properties. After separation, the individual diastereomers are converted back into the original enantiomers.

For example, because an acid reacts with a base to form a salt, a racemic mixture of a carboxylic acid reacts with a naturally occurring optically pure (a single enantiomer) base to form two diastereomeric salts. Morphine, strychnine, and brucine are examples of naturally occurring chiral bases commonly used for this purpose. The chiral base exists as a single enantiomer because when a chiral compound is synthesized in a living system, generally only one enantiomer is formed (Section 5.20). When an *R*-acid reacts with an *S*-base, an *R*,*S*-salt will be formed; when an *S*-acid reacts with an *S*-base, an *S*,*S*-salt will be formed.

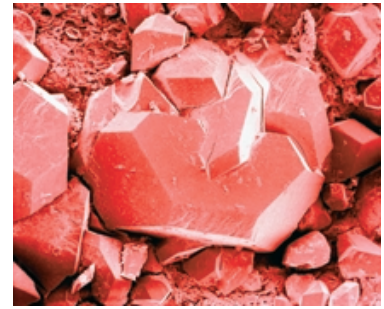


Eilhardt Mitscherlich (1794–1863), *a German chemist, first studied medicine so he could travel to Asia—a way to satisfy his interest in Oriental languages. He later became fascinated by chemistry. He was a professor of chemistry at the University of Berlin and wrote a successful chemistry textbook that was published in 1829.*

One of the asymmetric carbons in the *R*,*S*-salt is identical to an asymmetric carbon in the *S*,*S*-salt, and the other asymmetric carbon in the *R*,*S*-salt is the mirror image of an asymmetric carbon in the *S*,*S*-salt. Therefore, the salts are diastereomers and have dif-

ferent physical properties, so they can be separated. After separation, they can be converted back to the carboxylic acids by adding a strong acid such as HCl. The chiral base can be separated from the carboxylic acid and used again.

Enantiomers can also be separated by a technique called **chromatography**. In this method, the mixture to be separated is dissolved in a solvent and the solution is passed through a column packed with material that tends to adsorb organic compounds. If the chromatographic column is packed with *chiral* material, the two enantiomers can be expected to move through the column at different rates because they will have different affinities for the chiral material—just as a right hand prefers a right-hand glove—so one enantiomer will emerge from the column before the other. The chiral material is an example of a **chiral probe**—it can distinguish between enantiomers. A polarimeter is another example of a chiral probe (Section 5.7). In the next section you will see two kinds of biological molecules that are chiral probes—enzymes and receptors, both of which are proteins.



▲ Crystals of potassium hydrogen tartrate. Grapes are unusual in that they produce large quantities of tartaric acid, whereas most fruits produce citric acid.

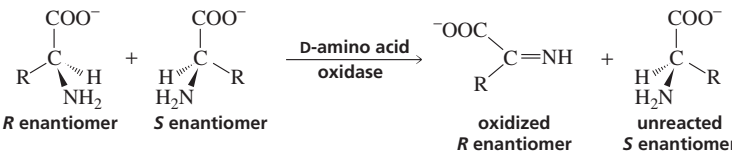
5.15 Discrimination of Enantiomers by Biological Molecules

Enzymes

Enantiomers can be separated easily if they are subjected to reaction conditions that cause only one of them to react. Enantiomers have the same chemical properties, so they react with *achiral* reagents at the same rate. Thus, hydroxide ion (an achiral reagent) reacts with (*R*)-2-bromobutane at the same rate that it reacts with (*S*)-2-bromobutane. However, *chiral* molecules recognize only one enantiomer, so if a synthesis is carried out using a chiral reagent or a chiral catalyst, only one enantiomer will undergo the reaction. One example of a **chiral catalyst** is an *enzyme*. An **enzyme** is a protein that catalyzes a chemical reaction. The enzyme D-amino acid oxidase, for example, catalyzes only the reaction of the *R* enantiomer and leaves the *S* enantiomer unchanged. The product of the enzyme-catalyzed reaction can be easily separated from the unreacted enantiomer. If you imagine an enzyme to be a right-hand glove and the enantiomers to be a pair of hands, the enzyme typically binds only one enantiomer because only the right hand fits into the right-hand glove.

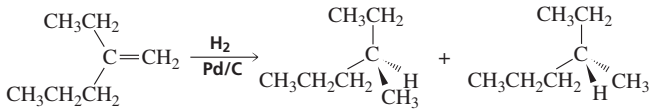
An achiral reagent reacts identically with both enantiomers. A sock, which is achiral, fits on either foot.

A chiral reagent reacts differently with each enantiomer. A shoe, which is chiral, fits on only one foot.



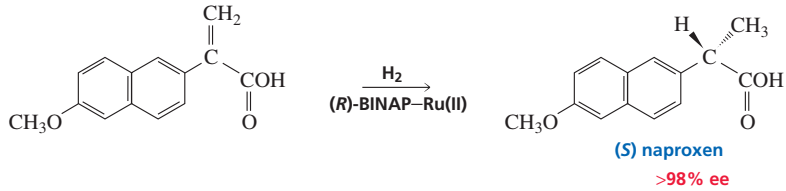
***R* enantiomer** ***S* enantiomer** **oxidized *R* enantiomer** **unreacted *S* enantiomer**

The problem of having to separate enantiomers can be avoided if a synthesis is carried out that forms one of the enantiomers preferentially. Non-enzymatic chiral catalysts are being developed that will synthesize one enantiomer in great excess over the other. If a reaction is carried out with a reagent that does not have an asymmetric carbon and forms a product with an asymmetric carbon, a racemic mixture of the product will be formed. For example, the catalytic hydrogenation of 2-ethyl-1-pentene forms equal amounts of the two enantiomers because H_2 can be delivered equally easily to both faces of the double bond (Section 5.18).



(*R*)-3-methylhexane **50%** **(*S*)-3-methylhexane** **50%**

If, however, the metal is complexed to a chiral organic molecule, H_2 will be delived to only one face of the double bond. One such chiral catalyst—using Ru(II) as the metal and BINAP (2,2′-bis(diphenylphosphino)-1,1′-binaphthyl) as the chiral molecule—has been used to synthesize (*S*)-naproxen, the active ingredient in Aleve and several other over-the-counter nonsteroidal anti-inflammatory drugs, in greater than 98% enantiomeric excess.



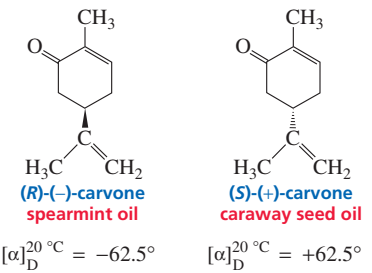
PROBLEM 38◆

What percent of naproxen is obtained as the *S* enantiomer in the above synthesis?

Receptors

A receptor is a protein that binds a particular molecule. Because a receptor is chiral, it will bind one enantiomer better than the other. In Figure 5.3 the receptor binds the *R* enantiomer but it does not bind the *S* enantiomer.

Because a receptor typically recognizes only one enantiomer, different physiological properties may be associated with each enantiomer. Receptors located on the exterior of nerve cells in the nose, for example, are able to perceive and differentiate the estimated 10,000 smells to which they are exposed. (*R*)-(−)-carvone is found in spearmint oil, and (*S*)-(+)-carvone is the main constituent of caraway seed oil. The reason these two enantiomers have such different odors is that each fits into a different receptor.



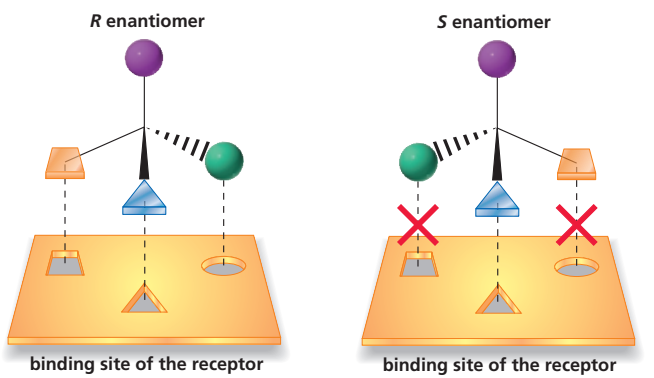
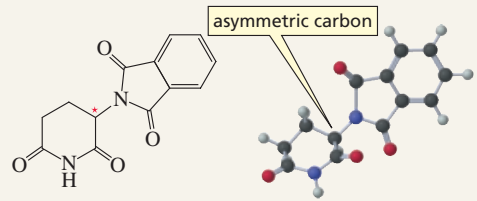


Figure 5.3 ▶
Schematic diagram showing why only one enantiomer is bound by a receptor. One enantiomer fits into the binding site and one does not.

Many drugs exert their physiological activity by binding to cellular receptors. If the drug has an asymmetric carbon, the receptor can preferentially bind one of the enantiomers. Thus, enantiomers can have the same physiological activities, different degrees of the same activity, or very different activities.

THE ENANTIOMERS OF THALIDOMIDE

Thalidomide was approved as a sedative for use in Europe and Canada in 1956. It was not approved for use in the United States because some neurological side effects had been noted. The dextrorotatory isomer has stronger sedative properties, but the commercial drug was a racemic mixture. However, it wasn't recognized that the levorotatory isomer was highly teratogenic—it causes horrible birth defects—until it was noticed that women who were given the drug during the first three months of pregnancy gave birth to babies with a wide variety of defects, such as deformed limbs. It was eventually determined that the dextrorotatory isomer also has mild teratogenic activity and that both enantiomers racemize in vivo. Thus, it is not clear whether giving those women only the dextrorotatory isomer would have decreased the severity of the birth defects. Thalidomide recently has been approved—with restrictions—to treat leprosy as well as melanomas.



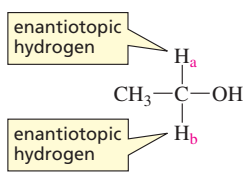
thalidomide

CHIRAL DRUGS

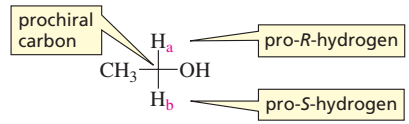
Until relatively recently, most drugs have been marketed as racemic mixtures because of the high cost of separating the enantiomers. In 1992, the Food and Drug Administration (FDA) issued a policy statement encouraging drug companies to use recent advances in synthetic and separation techniques to develop single enantiomer drugs. Now one-third of all drugs sold are single enantiomers. A new treatment for asthma is a single-enantiomer drug called Singulair. The antidepresanets Zoloft® and Paxil® (single enantiomers) are cutting into Prozac®'s (a racemate) market. Testing of single-enantiomer drugs is simpler because if a drug is sold as a racemate, the FDA requres that both enantiomers be tested. Testing has shown that (*S*)-(+)-ketamine is four times more potent an anesthetic than (*R*)-(−)-ketamine and, even more important, the disturbing side effects appear to be associated only with the (*R*)-(−)-enantiomer. The activity of ibuprofen, the popular analgesic marketed as Advil®, Nuprin®, and Motrin®, resides primarily in the (*S*)-(+)-enantiomer. The FDA has some concern about approving the drug as a single enantiomer because of potential drug overdoses. Can people who are used to taking two pills be convinced to take only one? Heroin addicts can be maintained with (−)-α-acetylmethadol for a 72-hour period compared to 24 hours with racemic methadone. This means less frequent visits to the clinic, and a single dose can get an addict through an entire weekend. Another reason for the increase in single-enantiomeric drugs is that drug companies may be able to extend their patents by developing a drug as a single enantiomer that was marketed previously as a racemate.

5.16 Enantiotopic Hydrogens, Diastereotopic Hydrogens, and Prochiral Carbons

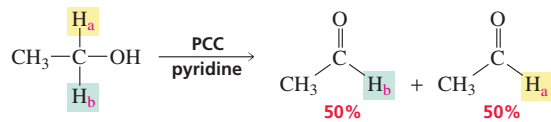
If a carbon is bonded to two hydrogens and to two different groups, the two hydrogens are called **enantiotopic hydrogens**. For example, the two hydrogens (H_a and H_b) in the CH_2 group of ethanol are enantiotopic hydrogens because the other two groups bonded to the carbon (CH_3 and OH) are not identical. Replacing an enantiotopic hydrogen by a deuterium (or any other atom or group other than CH_3 or OH) forms a chiral molecule.



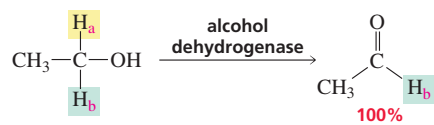
The carbon to which the enantiotopic hydrogens are attached is called a **prochiral carbon** because it will become a chirality center (an asymmetric carbon) if one of the hydrogens is replaced by a deuterium (or any group other than CH_3 or OH). If the H_a hydrogen is replaced by a deuterium, the asymmetric carbon will have the *R* configuration. Thus, the H_a hydrogen is called the **pro-*R*-hydrogen**. The H_b hydrogen is called the **pro-*S*-hydrogen** because if it is replaced by a deuterium, the asymmetric carbon will have the *S* configuration. The molecule containing the prochiral carbon is called a prochiral molecule because it would become a chiral molecule if one of the enantiotopic hydrogens is replaced.



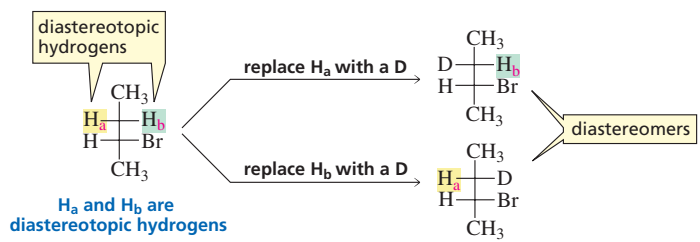
The pro-*R*- and pro-*S*-hydrogens are chemically equivalent, so they have the same chemical reactivity and cannot be distinguished by achiral reagents. For example, when ethanol is oxidized by pyridinium chlorochromate (PCC) to acetaldehyde, one of the enantiotopic hydrogens is removed. (PCC is discussed in Section 20.2.) Because the two hydrogens are chemically equivalent, half the product results from removing the H_a hydrogen and the other half results from removing the H_b hydrogen.



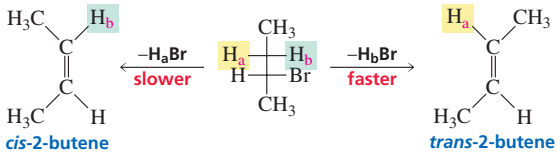
Enantiotopic hydrogens, however, are not chemically equivalent toward chiral reagents. An enzyme can distinguish between them because an enzyme is chiral (Section 5.15). For example, when the oxidation of ethanol to acetaldehyde is catalyzed by the enzyme alcohol dehydrogenase, only one of the enantiotopic hydrogens (H_a) is removed.



If a carbon is bonded to two hydrogens and replacing each of them in turn with deuterium (or another group) creates a pair of diastereomers, the hydrogens are called **diastereotopic hydrogens**.



Unlike enantiotopic hydrogens, diastereotopic hydrogens do not have the same reactivity with achiral reagents. For example, in Chapter 11 we will see that because *trans*-2-butene is more stable than *cis*-2-butene (Section 4.11), removal of H_b and Br to form *trans*-2-butene occurs more rapidly than removal of H_a and Br to form *cis*-2-butene.



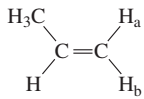
PROBLEM 39◆

Tell whether the H_a and H_b hydrogens in each of the following compounds are enantiotopic, diastereotopic, or neither.

a. $CH_3CH_2\overset{\overset{H_a}{|}}{\underset{\underset{H_b}{|}}{C}}CH_3$

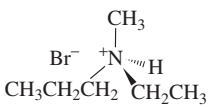
b.

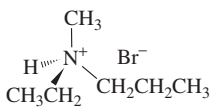
c.

d. 

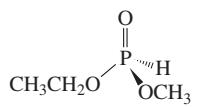
5.17 Nitrogen and Phosphorus Chirality Centers

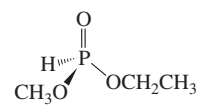
Atoms other than asymmetric carbons can be chirality centers. When an atom such as nitrogen or phosphorus has four different groups or atoms attached to it and it has a tetrahedral geometry, it is a chirality center. A compound with a chirality center can exist as enantiomers, and the enantiomers can be separated.





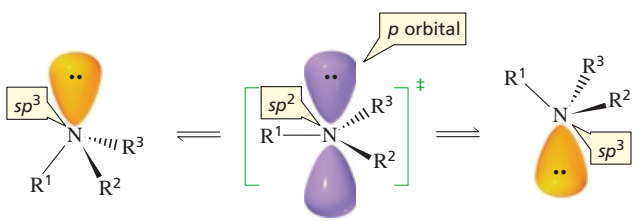
enantiomers





enantiomers

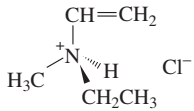
If one of the four "groups" attached to nitrogen is a lone pair, the enantiomers cannot be separated because they interconvert rapidly at room temperature. This is called **amine inversion** (Section 21.2). One way to picture amine inversion is to compare it to an umbrella that turns inside out in a windstorm.



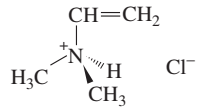
transition state

PROBLEM 40

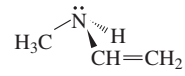
Compound A has two stereoisomers, but compounds B and C exist as single compounds. Explain.



A



B



C

5.18 Stereochemistry of Reactions: Regioselective, Stereoselective, and Stereospecific Reactions

In Chapter 4 we saw that alkenes undergo electrophilic addition reactions, and we looked at the different kinds of reagents that add to alkenes. We also examined the step-by-step process by which each reaction occurs (the mechanism of the reaction), and we determined what products are formed. However, we did not consider the stereochemistry of the reactions.

Stereochemistry is the field of chemistry that deals with the structures of molecules in three dimensions. When we study the stereochemistry of a reaction, we are concerned with the following questions:

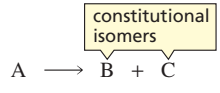
1. If a reaction product can exist as two or more stereoisomers, does the reaction produce a single stereoisomer, a set of particular stereoisomers, or all possible stereoisomers?
2. If stereoisomers are possible for the reactant, do all stereoisomers react to form the same stereoisomeric product, or does each reactant form a different stereoisomer or a different set of stereoisomers?

Before we examine the stereochemistry of electrophilic addition reactions, we need to become familiar with some terms used in describing the stereochemistry of a reaction.

A regioselective reaction forms more of one constitutional isomer than of another.

In Section 4.4 we saw that a **regioselective** reaction is one in which two *constitutional isomers* can be obtained as products but more of one is obtained than of the other. In other words, a regioselective reaction selects for a particular constitutional isomer. Recall that a reaction can be *moderately regioselective*, *highly regioselective*, or *completely regioselective* depending on the relative amounts of the constitutional isomers formed in the reaction.

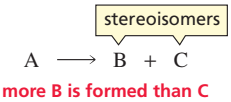
a regioselective reaction



more B is formed than C

Stereoselective is a similar term, but it refers to the preferential formation of a *stereoisomer* rather than a *constitutional isomer*. If a reaction that generates a carbon–carbon double bond or an asymmetric carbon in a product forms one stereoisomer preferentially over another, it is a stereoselective reaction. In other words, it selects for a particular stereoisomer. Depending on the degree of preference for a particular stereoisomer, a reaction can be described as being *moderately stereoselective*, *highly stereoselective*, or *completely stereoselective*.

a stereoselective reaction

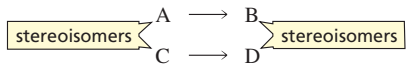


Tutorial: Common terms in stereochemistry

A stereoselective reaction forms more of one stereoisomer than of another.

A reaction is **stereospecific** if the reactant can exist as stereoisomers and each stereoisomeric reactant leads to a different stereoisomeric product or a different set of stereoisomeric products.

stereospecific reactions



In a stereospecific reaction each stereoisomer forms a different stereoisomeric product or a different set of stereoisomeric products.

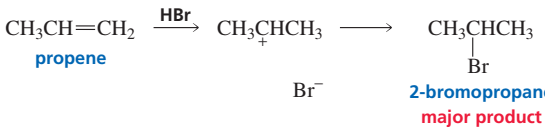
In the preceding reaction, stereoisomer A forms stereoisomer B but does not form D, so the reaction is stereoselective in addition to being stereospecific. *All stereospecific reactions, therefore, are also stereoselective. All stereoselective reactions are not stereospecific*, however, because there are stereoselective reactions in which the reactant does not have a carbon–carbon double bond or an asymmetric carbon, so it cannot exist as stereoisomers.

A stereospecific reaction is also stereoselective. A stereoselective reaction is not necessarily stereospecific.

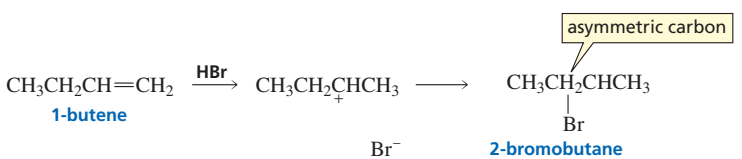
5.19 Stereochemistry of Electrophilic Addition Reactions of Alkenes

Now that you are familiar with electrophilic addition reactions and with stereoisomers, we can combine the two topics and look at the stereochemistry of electrophilic addition reactions. In other words, we will look at the stereoisomers that are formed in the electrophilic addition reactions that were discussed in Chapter 4.

In Chapter 4 we saw that when an alkene reacts with an electrophilic reagent such as HBr, the major product of the addition reaction is the one obtained by adding the electrophile (H^+) to the sp^2 carbon bonded to the greater number of hydrogens and adding the nucleophile (Br^-) to the other sp^2 carbon. For example, the major product obtained from the reaction of propene with HBr is 2-bromopropane. This particular product does not have stereoisomers because it does not have an asymmetric carbon. Therefore, we do not have to be concerned with the stereochemistry of this reaction.



If, however, the reaction creates a product with an asymmetric carbon, we need to know which stereoisomers are formed. For example, the reaction of HBr with 1-butene forms 2-bromobutane, a compound with an asymmetric carbon. What is the configuration of the product? Do we get the *R* enantiomer, the *S* enantiomer, or both?



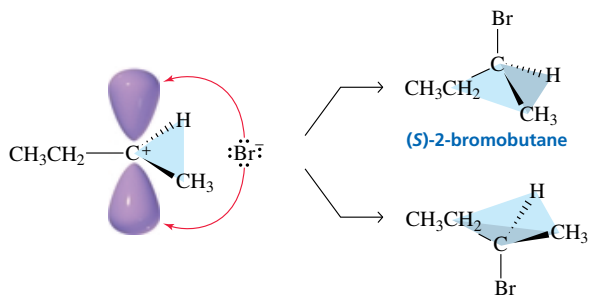
In discussing the stereochemistry of electrophilic addition reactions, we will look first at reactions that form a product with one asymmetric carbon. Then we will look at reactions that form a product with two asymmetric carbons.

Addition Reactions that Form One Asymmetric Carbon

When a reactant that does not have an asymmetric carbon undergoes a reaction that forms a product with *one* asymmetric carbon, the product will be a racemic mixture. For example, the reaction of 1-butene with HBr forms identical amounts of (*R*)-2-bromobutane and (*S*)-2-bromobutane. Thus, an electrophilic addition reaction that forms a compound with one asymmetric carbon from a reactant without any asymmetric carbons is not stereoselective because it does not select for a particular stereoisomer. Why is this so?

You will see why a racemic mixture is obtained if you examine the structure of the carbocation formed in the first step of the reaction. The positively charged carbon is sp^2 hybridized, so the three atoms to which it is bonded lie in a plane (Section 1.10). When the bromide ion approaches the positively charged carbon from above the plane, one enantiomer is formed, but when it approaches from below the plane, the other enantiomer is formed. Because the bromide ion has equal access to both sides of the plane, identical amounts of the *R* and *S* enantiomers are obtained from the reaction.

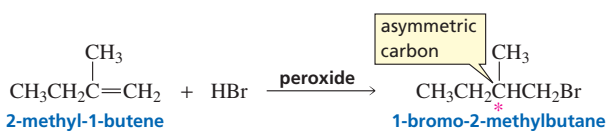
Tutorial:
Review addition of HBr
tutorial in Chapter 3



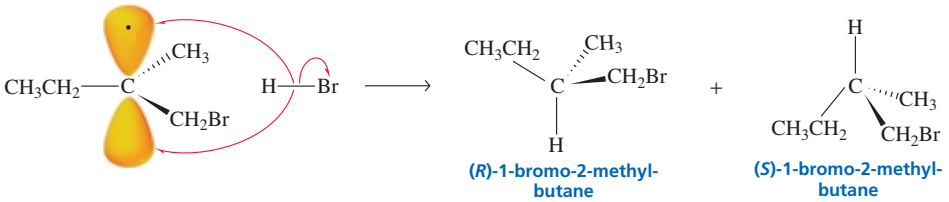
PROBLEM 41◆

a. Is the reaction of 2-butene with HBr regioselective?
b. Is it stereoselective?
c. Is it stereospecific?
d. Is the reaction of 1-butene with HBr regioselective?
e. Is it stereoselective?
f. Is it stereospecific?

When HBr adds to 2-methyl-1-butene in the presence of a peroxide, the product has one asymmetric carbon. Therefore, we can predict that identical amounts of the *R* and *S* enantiomers are formed.



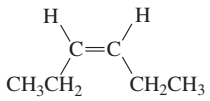
The product is a racemic mixture because the carbon in the radical intermediate that bears the unpaired electron is sp^2 hybridized. This means that the three atoms bonded to it are all in the same plane (Section 1.10). Consequently, identical amounts of the *R* enantiomer and the *S* enantiomer will be obtained because HBr has equal access to both sides of the radical. (Although the unpaired electron is shown to be in the top lobe of the *p* orbital, it actually is spread out equally through both lobes.)

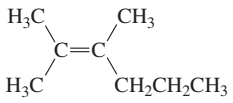


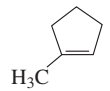
PROBLEM 42

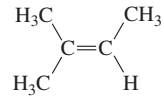
What stereoisomers are obtained from each of the following reactions?

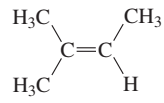
a. $CH_3CH_2CH_2CH{=}CH_2 \xrightarrow{HCl}$

b.  $\xrightarrow[H_2O]{H^+}$

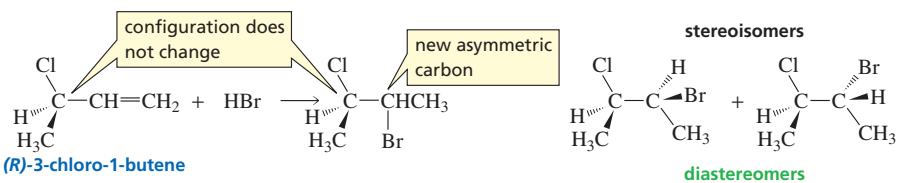
c.  $\xrightarrow[Pt/C]{H_2}$

d.  $\xrightarrow{HBr}$

e.  $\xrightarrow{HBr}$

f.  $\xrightarrow[\text{peroxide}]{HBr}$

If a reaction creates an asymmetric carbon in a compound that already has an asymmetric carbon, a pair of diastereomers will be formed. For example, let's look at the following reaction. Because none of the bonds to the asymmetric carbon in the reactant is broken during the addition of HBr, the configuration of this asymmetric carbon does not change. The bromide ion can approach the planar carbocation intermediate from either the top or the bottom in the process of creating the new asymmetric carbon, so two stereoisomers result. The stereoisomers are diastereomers because one of the asymmetric carbons has the same configuration in both isomers and the other has opposite configurations in the two isomers.



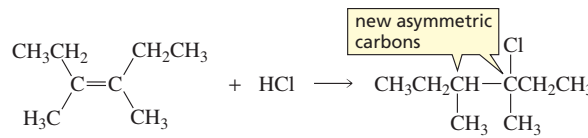
Because the products of the preceding reaction are diastereomers, the transition states that lead to them are also diastereomeric. The two transition states, therefore, will not have the same stability, so different amounts of the two diastereomers will be formed. The reaction is stereoselective—more of one stereoisomer is formed than of the other.

Addition Reactions that Form Products with Two Asymmetric Carbons

When a reactant that does not have an asymmetric carbon undergoes a reaction that forms a product with *two* asymmetric carbons, the stereoisomers that are formed depend on the mechanism of the reaction.

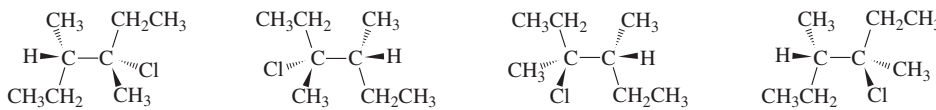
1. Addition Reactions that Form a Carbocation Intermediate or a Radical Intermediate

If two asymmetric carbons are created as the result of an addition reaction that forms a carbocation intermediate, four stereoisomers can be obtained as products.

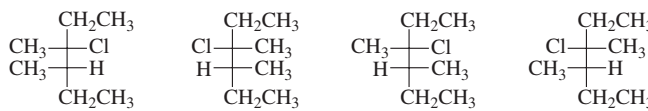


cis-3,4-dimethyl-3-hexene

3-chloro-3,4-dimethylhexane



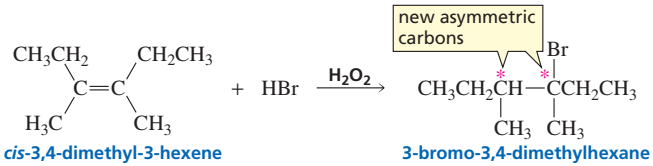
perspective formulas of the stereoisomers of the product

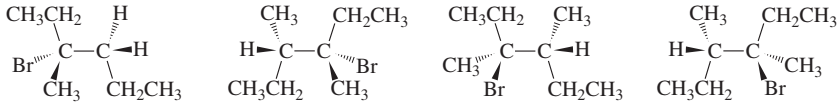


Fischer projections of the stereoisomers of the product

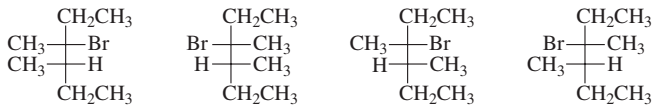
In the first step of the reaction, the proton can approach the plane containing the double-bonded carbons of the alkene from above or below to form the carbocation. Once the carbocation is formed, the chloride ion can approach the positively charged carbon from above or below. As a result, four stereoisomers are obtained as products: The proton and the chloride ion can add from above-above, above-below, below-above, or below-below. When the two substituents add to the same side of the double bond, the addition is called **syn addition**. When the two substituents add to opposite sides of the double bond, the addition is called **anti addition**. Both syn and anti addition occur in alkene addition reactions that take place by way of a carbocation intermediate. Because the four stereoisomers formed by the cis alkene are identical to the four stereoisomers formed by the trans alkene, the reaction is not stereospecific.

Similarly, if two asymmetric carbons are created as the result of an addition reaction that forms a radical intermediate, four stereoisomers can be formed because both syn and anti addition are possible. And because the stereoisomers formed by the cis isomer are identical to those formed by the trans isomer, the reaction is not stereospecific—in a stereospecific reaction, the cis and trans isomers form different stereoisomers.





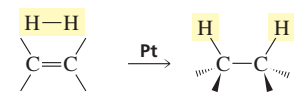
perspective formulas of the stereoisomers of the product



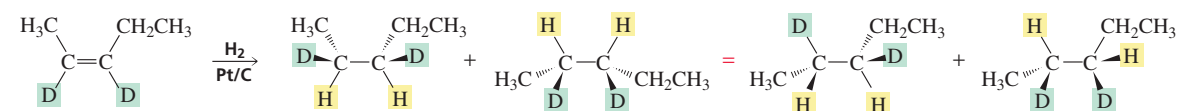
Fischer projections of the stereoisomers of the product

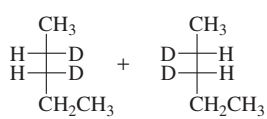
2. Stereochemistry of Hydrogen Addition

In a catalytic hydrogenation, the alkene sits on the surface of the metal catalyst and both hydrogen atoms add to the same side of the double bond (Section 4.11). Therefore, the addition of H_2 to an alkene is a syn addition reaction.



If addition of hydrogen to an alkene forms a product with two asymmetric carbons, only two of the four possible stereoisomers are obtained because only syn addition can occur. (The other two stereoisomers would have to come from anti addition.) One stereoisomer results from addition of both hydrogens from above the plane of the double bond, and the other stereoisomer results from addition of both hydrogens from below the plane. The particular pair of stereoisomers that is formed depends on whether the reactant is a *cis*-alkene or a *trans*-alkene. Syn addition of H_2 to a *cis*-alkene forms only the erythro enantiomers. (In Section 5.8, we saw that the erythro enantiomers are the ones with identical groups on the same side of the carbon chain in the eclisped conformers.)

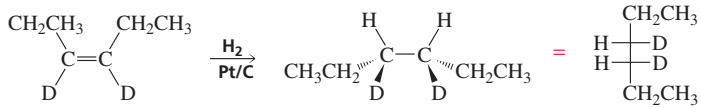




erythro enantiomers
Fischer projections

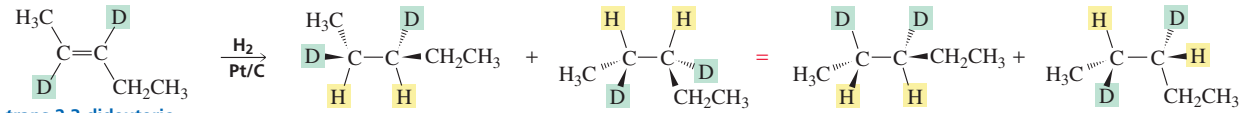
If you have trouble determining the configuration of a product, make a model.

If each of the two asymmetric carbons is bonded to the same four substituents, a meso compound will be obtained instead of the erythro enantiomers.



cis-2,3-dideuterio-2-pentene — meso compound

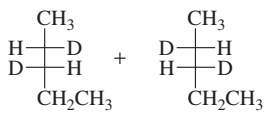
In contrast, syn addition of H_2 to a *trans*-alkene forms only the threo enantiomers. Thus the addition of hydrogen is a stereospecific reaction—the product obtained from addition to the cis isomer is different from the product obtained from addition to the trans isomer. It is also a stereoselective reaction because all possible isomers are not formed; for example, only the threo enantiomers are formed in the following reaction.



trans-2,3-dideuterio-2-pentene

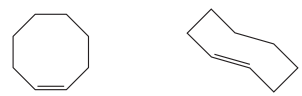
threo enantiomers
perspective formulas
(eclipsed conformers)

threo enantiomers
perspective formulas
(staggered conformers)



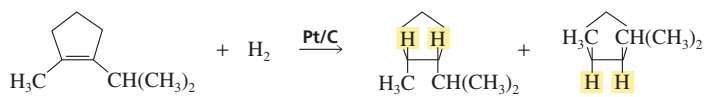
threo enantiomers
Fischer projections

Cyclic alkenes with fewer than eight carbons in the ring, such as cyclopentene and cyclohexene, can exist only in the cis configuration because they do not have enough carbons to incorporate a trans double bond. Therefore, it is not necessary to use the cis designation with their names. Both cis and trans isomers are possible for rings containing eight or more carbons, however, so the configuration of the compound must be specified in its name.



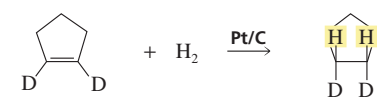
cis-cyclooctene — *trans*-cyclooctene

Therefore, the addition of H_2 to a cyclic alkene with fewer than eight ring atoms forms only the cis enantiomers.



1-isopropyl-2-methyl-cyclopentene

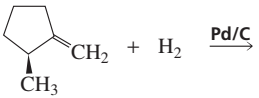
Each of the two asymmetric carbons in the product of the following reaction is bonded to the same four substituents. Therefore, syn addition forms a meso compound.



1,2-dideuterio-cyclopentene

PROBLEM 43

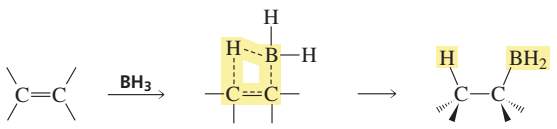
a. What stereoisomers are formed in the following reaction?



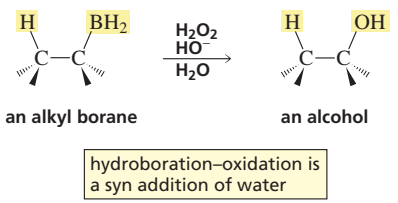
b. What stereoisomer is formed in greater yield?

3. Stereochemistry of Hydroboration–Oxidation

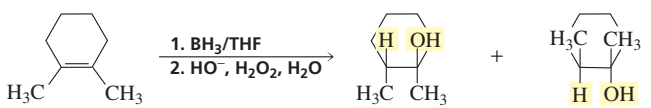
The addition of borane to an alkene is a concerted reaction. The boron and the hydride ion add to the two sp^2 carbons of the double bond at the same time (Section 4.9). Because the two species add simultaneously, they must add to the same side of the double bond. So the addition of borane to an alkene, like the addition of hydrogen, is a syn addition.



When the alkylborane is oxidized by reaction with hydrogen peroxide and hydroxide ion, the OH group ends up in the same position as the boron group it replaces. Consequently, the overall hydroboration–oxidation reaction amounts to a syn addition of water to a carbon–carbon double bond.



Because only syn addition occurs, hydroboration–oxidation is stereoselective—only two of the four possible stereoisomers are formed. As we saw when we looked at the addition of H_2 to a cycloalkene, syn addition results in the formation of only the pair of enantiomers that has the added groups on the same side of the ring.



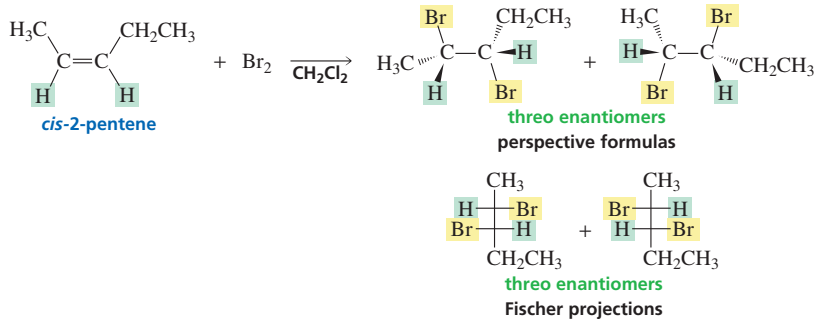
PROBLEM 44◆

What stereoisomers would be obtained from hydroboration–oxidation of the following compounds?

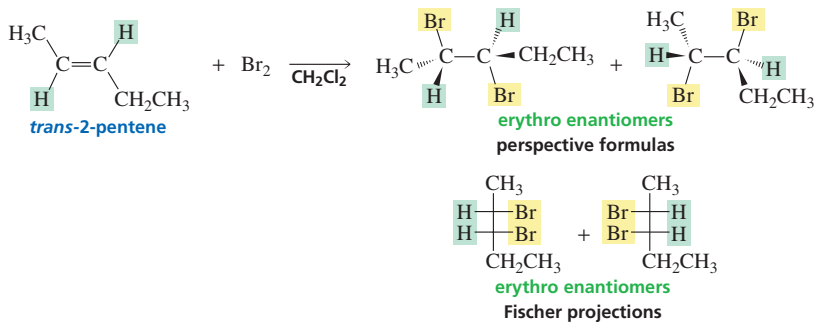
a. cyclohexene
b. 1-ethylcyclohexene
c. 1,2-dimethylcyclopentene
d. *cis*-2-butene

4. Addition Reactions that Form a Bromonium Ion Intermediate

If two asymmetric carbons are created as the result of an addition reaction that forms a bromonium ion intermediate, only one pair of enantiomers will be formed. In other words, the addition of Br_2 is a stereoselective reaction. The addition of Br_2 to the cis alkene forms only the threo enantiomers.

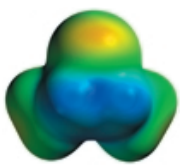


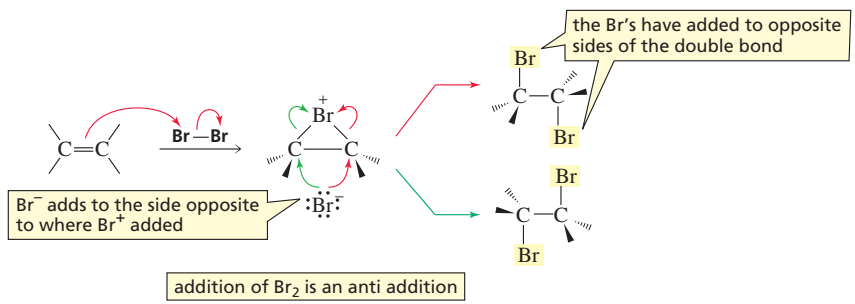
Similarly, the addition of Br_2 to the trans alkene forms only the erythro enantiomers. Because the cis and trans isomers form different products, the reaction is stereospecific as well as stereoselective.



Because the addition of Br_2 to the cis alkene forms the threo enantiomers, we know that addition of Br_2 is an example of anti addition because if syn addition had occurred to the cis alkene, the erythro enantiomers would have been formed. The addition of Br_2 is anti because the reaction intermediate is a cyclic bromonium ion (Section 4.7). Once the bromonium ion is formed, the bridged bromine atom blocks that side of the ion. As a result, the negatively charged bromide ion must approach from the opposite side (following either the green arrows *or* the red arrows). Thus, the two bromine atoms add to opposite sides of the double bond. Because only anti addition of Br_2 can occur, only two of the four possible stereoisomers are obtained.

Tutorial:
Review halogenation


the bromonium ion formed from the reaction of Br_2 with *cis*-2-butene



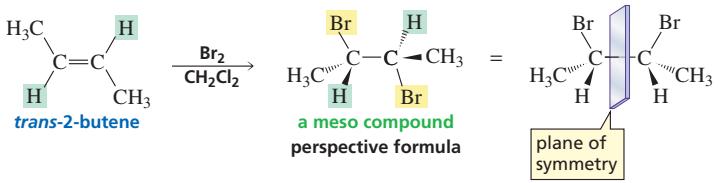
PROBLEM 45

Reaction of 2-ethyl-1-pentene with Br_2, with H_2/Pt, or with BH_3 followed by $HO^- + H_2O_2$ leads to a racemic mixture. Explain why a racemic mixture is obtained in each case.

PROBLEM 46

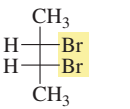
How could you prove, using a sample of *trans*-2-butene, that addition of Br_2 forms a cyclic bromonium ion intermediate rather than a carbocation intermediate?

If the two asymmetric carbons in the product each have the same four substituents, the erythro isomers are identical and constitute a meso compound. Therefore, addition of Br_2 to *trans*-2-butene forms a meso compound.



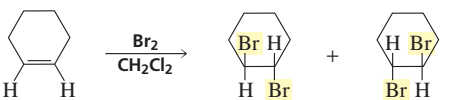
trans-2-butene

a meso compound
perspective formula



a meso compound
Fischer projection

Because only anti addition occurs, addition of Br_2 to a cyclohexene forms only the enantiomers that have the added bromine atoms on opposite sides of the ring.



One way to determine what stereoisomers are obtained from many reactions that create a product with two asymmetric carbons is the mnemonic **CIS-SYN-ERYTHRO**, which is easy to remember because all three terms mean "on the same side." You can change any two of the terms but you can't change just one. (For example, **TRANS-ANTI-ERYTHRO**, **TRANS-SYN-ERYTHREO**, and **CIS-ANTI-THREO** are allowed, but **TRANS-SYN-ERYTHRO** is not allowed.) So if you have a trans reactant that undergoes addition of Br_2 (which is anti), the erythro products are obtained. This mnemonic will work for all reactions that have a product with a structure that can be described by erythro or threo.

A summary of the stereochemistry of the products obtained from addition reactions to alkenes is given in Table 5.2.

PROBLEM-SOLVING STRATEGY

Give the configuration of the products obtained from the following reactions:

a. 1-butene + HCl
b. 1-butene + HBr + peroxide
c. 3-methyl-3-hexene + HBr + peroxide
d. *cis*-3-heptene + Br_2
e. *trans*-3-heptene + Br_2
f. *trans*-3-hexene + Br_2

Table 5.2 Stereochemistry of Alkene Addition Reactions

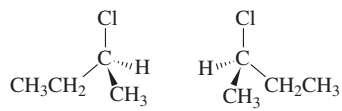
Reaction	Type of addition	Stereoisomers formed
Addition reactions that create one asymmetric carbon in the product		1. If the reactant does not have an asymmetric carbon, a pair of enantiomers will be obtained (equal amounts of the *R* and *S* isomers). 2. If the reactant has an asymmetric carbon, unequal amounts of a pair of diastereomers will be obtained.
Addition reactions that create two asymmetric carbons in the product		
Addition of reagents that form a carbocation or radical intermediate	syn and anti	Four stereoisomers can be obtained[a] (the cis and trans isomers form the same products)
Addition of H_2 Addition of borane	syn	cis ⟶ erythro enantiomers[a] trans ⟶ threo enantiomers
Addition of Br_2	anti	cis ⟶ threo enantiomers trans ⟶ erythro enantiomers[a]

[a] If the two asymmetric carbons have the same substituents, a meso compound will be obtained instead of the pair of erythro enantiomers.

Start by drawing the product without regard to its configuration, to check whether the reaction has created any asymmetric carbons. Then determine the configuration of the products, paying attention to the configuration (if any) of the reactant, how many asymmetric carbons are formed, and the mechanism of the reaction. Let's start with a.

a. $CH_3CH_2\underset{\displaystyle Cl}{\underset{|}{C}}HCH_3$

The product has one asymmetric carbon, so equal amounts of the *R* and *S* enantiomers will be formed.

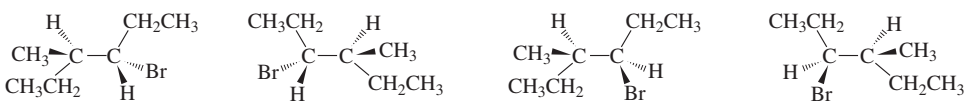


b. $CH_3CH_2CH_2CH_2Br$

The product does not have an asymmetric carbon, so it has no stereoisomers.

c. $CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}H\underset{\displaystyle Br}{\underset{|}{C}}HCH_2CH_3$

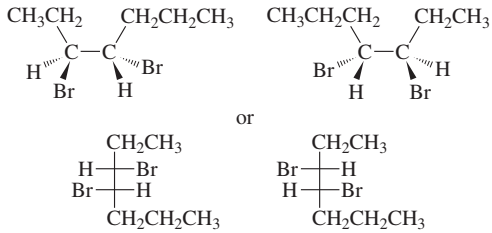
Two asymmetric carbons have been created in the product. Because the reaction forms a radical intermediate, two pairs of enantiomers are formed.



or

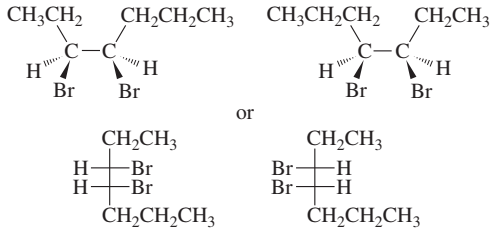
d. $CH_3CH_2\underset{\displaystyle Br}{\underset{|}{C}}H\underset{\displaystyle Br}{\underset{|}{C}}HCH_2CH_2CH_3$

Two asymmetric carbons have been created in the product. Because the reactant is cis and addition of Br_2 is anti, the threo enantiomers are formed.



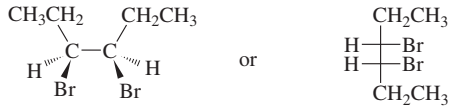
e. $CH_3CH_2\underset{\displaystyle Br}{\underset{|}{C}}H\underset{\displaystyle Br}{\underset{|}{C}}HCH_2CH_2CH_3$

Two asymmetric carbons have been created in the product. Because the reactant is trans and addition of Br_2 is anti, the erythro enantiomers are formed.



f. $CH_3CH_2\underset{\displaystyle Br}{\underset{|}{C}}H\underset{\displaystyle Br}{\underset{|}{C}}HCH_2CH_3$

Two asymmetric carbons have been created in the product. Because the reactant is trans and addition of Br_2 is anti, one would expect the erythro enantiomers. However, the two asymmetric carbons are bonded to the same four groups, so the erythro product is a meso compound. Thus, only one stereoisomer is formed.



Now continue on to Problem 47.

PROBLEM 47

Give the configuration of the products obtained from the following reactions:

a. *trans*-2-butene + HBr + peroxide
b. (*Z*)-3-methyl-2-pentene + HBr
c. (*Z*)-3-methyl-2-pentene + HBr + peroxide
d. *cis*-3-hexene + HBr
e. *cis*-2-pentene + Br_2
f. 1-hexene + Br_2

PROBLEM 48

When Br_2 adds to an alkene with different substituents on each of the two sp^2 carbons, such as *cis*-2-heptene, identical amounts of the two threo enantiomers are obtained even though Br^- is more likely to attack the less sterically hindered carbon atom of the bromonium ion. Explain why identical amounts of the stereoisomers are obtained.

PROBLEM 49

a. What products would be obtained from the addition of Br_2 to cyclohexene if the solvent were H_2O instead of CH_2Cl_2?

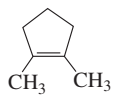
b. Propose a mechanism for the reaction.

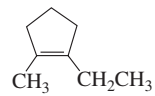
PROBLEM 50

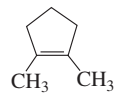
What stereoisomers would you expect to obtain from each of the following reactions?

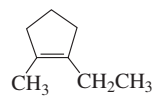
a. CH_3CH_2, CH_3, $C{=}C$, CH_3, CH_2CH_3 $\xrightarrow[CH_2Cl_2]{Br_2}$

b. CH_3CH_2, CH_3, $C{=}C$, H_3C, CH_2CH_3 $\xrightarrow[Pt/C]{H_2}$

c.  $\xrightarrow[CH_2Cl_2]{Br_2}$

d.  $\xrightarrow[CH_2Cl_2]{Br_2}$

e.  $\xrightarrow[Pt/C]{H_2}$

f.  $\xrightarrow[Pt/C]{H_2}$

PROBLEM 51◆

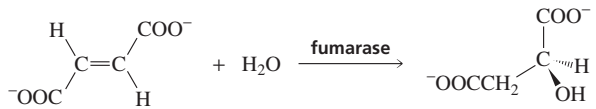
a. What is the major product obtained from the reaction of propene and Br_2 plus excess Cl^-?

b. Indicate the relative amounts of the stereoisomers obtained.

5.20 Stereochemistry of Enzyme-Catalyzed Reactions

The chemistry associated with living organisms is called **biochemistry**. When you study biochemistry, you study the structures and functions of the molecules found in the biological world and the reactions involved in the synthesis and degradation of these molecules. Because the compounds in living organisms are organic compounds, it is not surprising that many of the reactions encountered in organic chemistry are also seen when you study the chemistry of biological systems. Living cells do not contain molecules such as Cl_2, HBr, or BH_3, so you would not expect to find the addition of such reagents to alkenes in biological systems. However, living cells do contain water and acid catalysts, so some alkenes found in biological systems undergo the acid-catalyzed addition of water (Section 4.5).

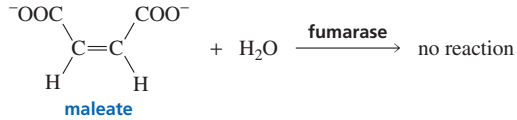
The organic reactions that occur in biological systems are catalyzed by enzymes. Enzyme-catalyzed reactions are almost always completely stereoselective. In other words, enzymes catalyze reactions that form only a single stereoisomer. For example, the enzyme fumarase, which catalyzes the addition of water to fumarate, forms only (*S*)-malate—the *R* enantiomer is not formed.



fumarate (*S*)-malate

An enzyme-catalyzed reaction forms only one stereoisomer because the binding site of an enzyme is chiral. The chiral binding site restricts delivery of reagents to only one side of the functional group of the reactant. Consequently, only one stereoisomer is formed.

Enzyme-catalyzed reactions are also stereospecific—an enzyme typically catalyzes the reaction of only one stereoisomer. For example, fumarase catalyzes the addition of water to fumarate (the trans isomer) but not to maleate (the cis isomer).



An enzyme is able to differentiate between stereoisomeric reactants because of its chiral binding site. The enzyme will bind only the stereoisomer whose substituents are in the correct positions to interact with substituents in the chiral binding site (Figure 5.3). Other stereoisomers do not have substituents in the proper positions, so they cannot bind efficiently to the enzyme. An enzyme's stereospecificity can be likened to a right-handed glove which fits only the right hand.

PROBLEM 52◆

a. What would be the product of the reaction of fumarate and H_2O if H^+ were used as a catalyst instead of fumarase?

b. What would be the product of the reaction of maleate and H_2O if H^+ were used as a catalyst instead of fumarase?

For studies on the stereochemistry of enzyme-catalyzed reactions, **Sir John Cornforth** *received the Nobel Prize in chemistry in 1975 (sharing it with Vladimir Prelog, page 188). Born in Australia in 1917, he studied at the University of Sydney and received a Ph.D. from Oxford. His major research was carried out in laboratories at Britain's Medical Research Council and in laboratories at Shell Research Ltd. He was knighted in 1977.*

Fundamental work on the stereochemistry of enzyme-catalyzed reactions was done by **Frank H. Westheimer**. *Westheimer was born in Baltimore in 1912 and received his graduate training at Harvard University. He served on the faculty of the University of Chicago and subsequently returned to Harvard as a professor of chemistry.*

Summary

Stereochemistry is the field of chemistry that deals with the structures of molecules in three dimensions. Compounds that have the same molecular formula but are not identical are called **isomers**; they fall into two classes: constitutional isomers and stereoisomers. **Constitutional isomers** differ in the way their atoms are connected. **Stereoisomers** differ in the way their atoms are arranged in space. There are two kinds of stereoisomers: **cis–trans isomers** and isomers that contain chirality centers.

A **chiral** molecule has a nonsuperimposable mirror image. An **achiral** molecule has a superimposable mirror image. The feature that is most often the cause of chirality is an asymmetric carbon. An **asymmetric carbon** is a carbon bonded to four different atoms or groups. An asymmetric carbon is also known as a **chirality center**. Nitrogen and phosphorus atoms can also be chirality centers. Nonsuperimposable mirror-image molecules are called **enantiomers**. **Diastereomers** are stereoisomers that are not enantiomers. Enantiomers have identical physical and chemical properties; diastereomers have different physical and chemical properties. An achiral reagent reacts identically with both enantiomers; a chiral reagent reacts differently with each enantiomer. A mixture of equal amounts of two enantiomers is called a **racemic mixture**.

A **stereocenter** is an atom at which the interchange of two groups produces a stereoisomer: asymmetric carbons—where the interchange of two groups produces an enantiomer—and the carbons where the interchange of two groups converts a cis isomer to a trans isomer (or an *E* isomer to a *Z* isomer)—are stereocenters. The letters ***R*** and ***S*** indicate the **configuration** about an asymmetric carbon. If one molecule has the *R* and the other has the *S* configuration, they are enantiomers; if they both have the *R* or both have the *S* configuration, they are identical.

Chiral compounds are **optically active**—they rotate the plane of polarized light; achiral compounds are **optically inactive**. If one enantiomer rotates the plane of polarization clockwise (+), its mirror image will rotate the plane of polarization the same amount counterclockwise (−). Each optically active compound has a characteristic **specific rotation**. A **racemic mixture** is optically inactive. A **meso compound** has two or more asymmetric carbons and a plane of symmetry; it is an achiral molecule. A compound with the same four groups bonded to two different asymmetric carbons will have three stereoisomers, a meso compound and a pair of enantiomers. If a reaction does not break any bonds to the asymmetric carbon, the reactant and product will have the same **relative configuration**—their substituents will have the same relative positions. The **absolute configuration** is the actual configuration. If a reaction does break a bond to the asymmetric carbon, the configuration of the product will depend on the mechanism of the reaction.

A **regioselective** reaction selects for a particular constitutional isomer; a **stereoselective** reaction selects for a particular stereoisomer. A reaction is **stereospecific** if the reactant can exist as stereoisomers and each stereoisomeric reactant leads to a different stereoisomeric product or a

different set of stereoisomeric products. When a reactant that does not have an asymmetric carbon forms a product with one asymmetric carbon, the product will be a racemic mixture.

In **syn addition** the two substituents add to the same side of the double bond; in **anti addition** they add to opposite sides of the double bond. Both syn and anti addition occur in electrophilic addition reactions that take place by way of a carbocation or a radical intermediate. Addition of H_2 to an alkene is a syn addition reaction. Hydroboration–oxidation is overall a syn addition of water. Addition of Br_2 is an anti addition reaction. An enzyme-catalyzed reaction forms only one stereoisomer; an enzyme typically catalyzes the reaction of only one stereoisomer.

Key Terms

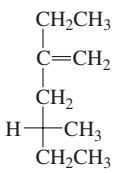
absolute configuration (p. 209)
achiral (p. 184)
amine inversion (p. 217)
anti addition (p. 222)
asymmetric carbon (p. 184)
biochemistry (p. 230)
chiral (p. 184)
chiral catalyst (p. 213)
chiral probe (p. 213)
chirality center (p. 185)
cis isomer (p. 183)
cis–trans isomers (p. 182)
chromatography (p. 213)
configuration (p. 188)
configurational isomers (p. 182)
constitutional isomers (p. 182)
dextrorotatory (p. 193)
diastereomer (p. 197)
diastereotopic hydrogens (p. 216)
enantiomer (p. 186)
enantiomerically pure (p. 195)
enantiomeric excess (ee) (p. 196)
enantiotopic hydrogens (p. 215)
enzyme (p. 213)
erythro enantiomers (p. 198)
Fischer projection (p. 187)
geometric isomers (p. 183)
isomers (p. 182)
levorotatory (p. 193)
meso compound (p. 201)
observed rotation (p. 194)
optical purity (op) (p. 195)
optically active (p. 193)
optically inactive (p. 193)
perspective formula (p. 186)
plane of symmetry (p. 201)
plane-polarized light (p. 192)
polarimeter (p. 193)
prochiral carbon (p. 216)
pro-*R* hydrogen (p. 216)
pro-*S* hydrogen (p. 216)
racemate (p. 195)
racemic mixture (p. 195)
R configuration (p. 188)
regioselective (p. 218)
relative configuration (p. 209)
resolution of a racemic mixture (p. 212)
S configuration (p. 188)
specific rotation (p. 194)
stereocenter (p. 187)
stereochemistry (p. 218)
stereoisomers (p. 182)
stereoselective (p. 218)
stereospecific (p. 219)
syn addition (p. 222)
threo enantiomers (p. 198)
trans isomer (p. 183)

Problems

53. Neglecting stereoisomers, give the structures of all compounds with molecular formula C_5H_{10}. Which ones can exist as stereoisomers?

54. Draw all possible stereoisomers for each of the following compounds. State if no stereoisomers are possible.
    a. 1-bromo-2-chlorocyclohexane
    b. 2-bromo-4-methylpentane
    c. 1,2-dichlorocyclohexane
    d. 2-bromo-4-chloropentane
    e. 3-heptene
    f. 1-bromo-4-chlorocyclohexane
    g. 1,2-dimethylcyclopropane
    h. 4-bromo-2-pentene
    i. 3,3-dimethylpentane
    j. 3-chloro-1-butene
    k. 1-bromo-2-chlorocyclobutane
    l. 1-bromo-3-chlorocyclobutane

55. Name each of the following compounds using *R*,*S* and *E*,*Z* (Section 3.5) designations where necessary:

a.


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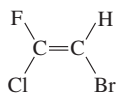
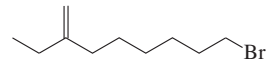
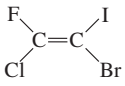
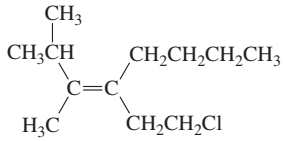
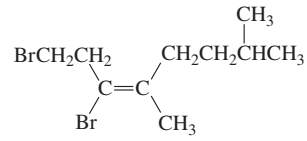
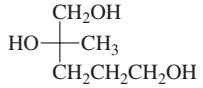


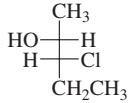
e.


b.


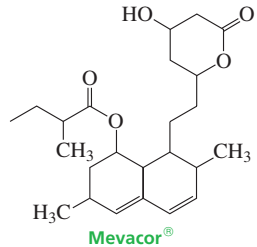
d.


f.


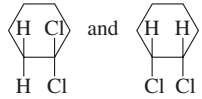
g. 

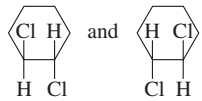
h. 

56. Mevacor® is used clinically to lower serum cholesterol levels. How many asymmetric carbons does Mevacor® have?

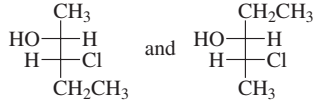


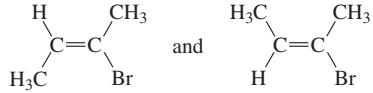
57. Indicate whether each of the following pairs of compounds are identical or are enantiomers, diastereomers, or constitutional isomers:

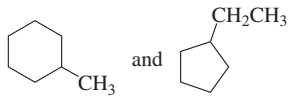
a. 

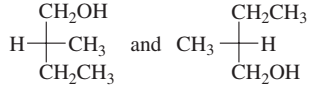
b. 

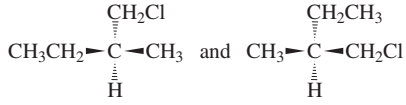
c.

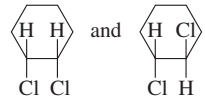
d. 

e. 

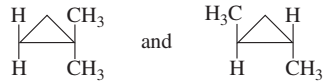
f. 

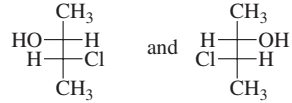
g. 

h. 

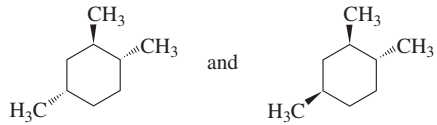
i. 

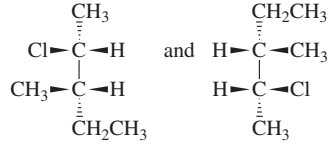
j.

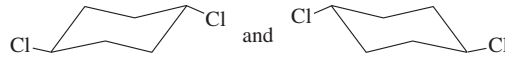
k. 

l. 

m.

n. 

o. 

p. 

58. a. Give the product(s) that would be obtained from the reaction of *cis*-2-butene and *trans*-2-butene with each of the following reagents. If the products can exist as stereoisomers, show which stereoisomers are obtained.

1. HCl
2. BH_3/THF followed by HO^-, H_2O_2
3. HBr + peroxide
4. Br_2 in CH_2Cl_2
5. $Br_2 + H_2O$
6. H_2/Pt/C
7. $HCl + H_2O$
8. $HCl + CH_3OH$

b. With which reagents do the two alkenes react to give different products?

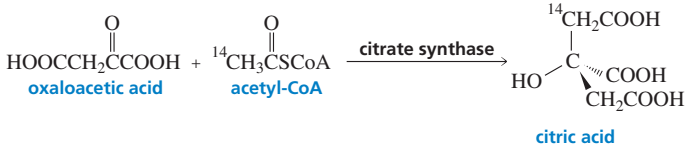
59. Which of the following compounds have an achiral stereoisomer?

a. 2,3-dichlorobutane
b. 2,3-dichloropentane
c. 2,3-dichloro-2,3-dimethylbutane
d. 1,3-dichlorocyclopentane
e. 1,3-dibromocyclobutane
f. 2,4-dibromopentane
g. 2,3-dibromopentane
h. 1,4-dimethylcyclohexane
i. 1,2-dimethylcyclopentane
j. 1,2-dimethylcyclobutane

60. Give the products and their configurations obtained from the reaction of 1-ethylcyclohexene with the following reagents:

a. HBr
b. HBr + peroxide
c. H_2, Pt/C
d. BH_3/THF followed by HO^-, H_2O_2
e. Br_2/CH_2Cl_2

61. Citrate synthase, one of the enzymes in the series of enzyme-catalyzed reactions known as the Krebs cycle, catalyzes the synthesis of citric acid from oxaloacetic acid and acetyl-CoA. If the synthesis is carried out with acetyl-CoA that has radioactive carbon (^{14}C) in the indicated position, the isomer shown here is obtained.



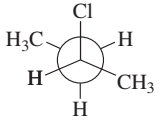
a. Which stereoisomer of citric acid is synthesized, *R* or *S*?
b. Why is the other stereoisomer not obtained?
c. If the acetyl-CoA used in the synthesis does not contain ^{14}C, will the product of the reaction be chiral or achiral?

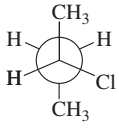
62. Give the products of the following reactions. If the products can exist as stereoisomers, show which stereoisomers are obtained.

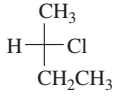
a. *cis*-2-pentene + HCl
b. *trans*-2-pentene + HCl
c. 1-ethylcyclohexene + H_3O^+
d. 1,2-diethylcyclohexene + H_3O^+
e. 1,2-dimethylcyclohexene + HCl
f. 1,2-dideuteriocyclohexene + H_2, Pt/C
g. 3,3-dimethyl-1-pentene + Br_2/CH_2Cl_2
h. (*E*)-3,4-dimethyl-3-heptene + H_2, Pt/C
i. (*Z*)-3,4-dimethyl-3-heptene + H_2, Pt/C
j. 1-chloro-2-ethylcyclohexene + H_2, Pt/C

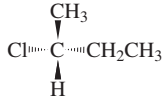
63. The specific rotation of (*R*)-(+)-glyceraldehyde is +8.7°. If the observed specific rotation of a mixture of (*R*)-glyceraldehyde and (*S*)-glyceraldehyde is +1.4°, what percent of glyceraldehyde is present as the *R* enantiomer?

64. Indicate whether each of the following structures is (*R*)-2-chlorobutane or (*S*)-2-chlorobutane. (Use models, if necessary.)

a. 

b. 

c. 

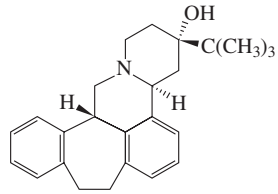
d. 

e.

f.

65. A solution of an unknown compound (3.0 g of the compound in 20 mL of solution), when placed in a polarimeter tube 2.0 dm long, was found to rotate the plane of polarized light 1.8° in a counterclockwise direction. What is the specific rotation of the compound?

66. Butaclamol is a potent antipsychotic that has been used clinically in the treatment of schizophrenia. How many asymmetric carbons does Butaclamol® have?



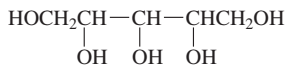
Butaclamol®

67. Which of the following objects are chiral?
    a. a mug with DAD written on one side
    b. a mug with MOM written on one side
    c. a mug with DAD written opposite the handle
    d. a mug with MOM written opposite the handle
    e. an automobile
    f. a wineglass
    g. a nail
    h. a screw

68. Explain how *R* and *S* are related to (+) and (−).

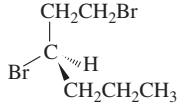
69. Give the products of the following reactions. If the products can exist as stereoisomers, show which stereoisomers are obtained.
    a. *cis*-2-pentene + Br_2/CH_2Cl_2
    b. *trans*-2-pentene + Br_2/CH_2Cl_2
    c. 1-butene + HCl
    d. 1-butene + HBr + peroxide
    e. *trans*-3-hexene + Br_2/CH_2Cl_2
    f. *cis*-3-hexene + Br_2/CH_2Cl_2
    g. 3,3-dimethyl-1-pentene + HBr
    h. *cis*-2-butene + HBr + peroxide
    i. (*Z*)-2,3-dichloro-2-butene + H_2, Pt/C
    j. (*E*)-2,3-dichloro-2-butene + H_2, Pt/C
    k. (*Z*)-3,4-dimethyl-3-hexene + H_2, Pt/C
    l. (*E*)-3,4-dimethyl-3-hexene + H_2, Pt/C

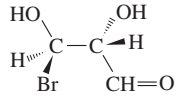
70. a. Draw all possible stereoisomers for the following compound.

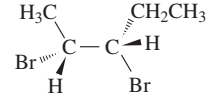


    b. Which isomers are optically inactive (will not rotate plane-polarized light)?

71. Indicate the configuration of the asymmetric carbons in the following molecules:

a. 

b. 

c. 

72. a. Draw all the isomers with molecular formula C_6H_{12} that contain a cyclobutane ring. (*Hint:* There are seven.)
    b. Name the compounds without specifying the configuration of any asymmetric carbons.
    c. Identify:
        1. constitutional isomers
        2. stereoisomers
        3. cis–trans isomers
        4. chiral compounds
        5. achiral compounds
        6. meso compounds
        7. enantiomers
        8. diastereomers

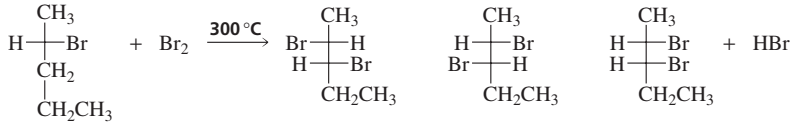
73. A compound has a specific rotation of −39.0°. A solution of the compound (0.187 g/mL) has an observed rotation of −6.52° when placed in a polarimeter tube 10 cm long. What is the percent of each enantiomer in the solution?

74. Draw structures for each of the following molecules:
    a. (*S*)-1-bromo-1-chlorobutane
    b. (2*R*,3*R*)-2,3-dichloropentane
    c. an achiral isomer of 1,2-dimethylcyclohexane
    d. a chiral isomer of 1,2-dibromocyclobutane
    e. two achiral isomers of 3,4,5-trimethylheptane

75. The enantiomers of 1,2-dimethylaziridine can be separated even though one of the "groups" attached to nitrogen is a lone pair. Explain.

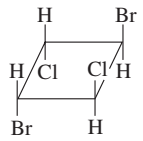
enantiomers of 1,2-dimethylaziridine

76. Of the possible monobromination products shown for the following reaction, circle any that would not be formed.

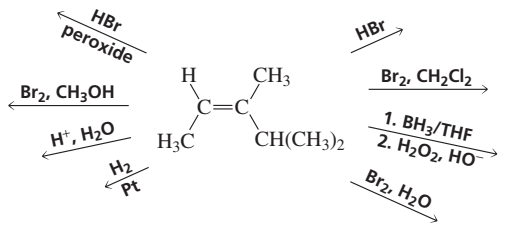


77. A sample of (*S*)-(+)-lactic acid was found to have an optical purity of 72%. How much *R* isomer is present in the sample?

78. Is the following compound optically active?

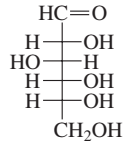


79. Give the products of the following reactions and their configurations:



80. a. Using the wedge-and-dash notation, draw the nine stereoisomers of 1,2,3,4,5,6-hexachlorocyclohexane.
    b. From the nine stereoisomers, identify one pair of enantiomers.
    c. Draw the most stable conformation of the most stable stereoisomer.

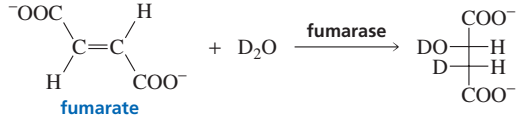
81. Sherry O. Eismer decided that the configuration of the asymmetric carbons in a sugar such as D-glucose could be determined rapidly by simply assigning the *R* configuration to an asymmetric carbon with an OH group on the right and the *S* configuration to an asymmetric carbon with an OH group on the left. Is she correct? (We will see in Chapter 22 that the "D" in D-glucose means the OH group on the bottommost asymmetric carbon is on the right.)



D-glucose

82. Cyclohexene exists only in the cis form, while cyclodecene exists in both the cis and trans forms. Explain. (*Hint:* Molecular models are helpful for this problem.)

83. When fumarate reacts with D_2O in the presence of the enzyme fumarase, only one isomer of the product is formed. Its structure is shown. Is the enzyme catalyzing a syn or an anti addition of D_2O?

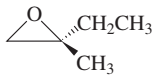


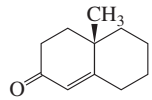
fumarate

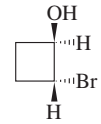
84. Two stereoisomers are obtained from the reaction of HBr with (*S*)-4-bromo-1-pentene. One of the stereoisomers is optically active, and the other is not. Give the structures of the stereoisomers, indicating their absolute configurations, and explain the difference in optical properties.

85. When (*S*)-(+)-1-chloro-2-methylbutane reacts with chlorine, one of the products formed is (−)-1,4-dichloro-2-methylbutane. Does this product have the *R* or the *S* configuration?

86. Indicate the configuration of the asymmetric carbons in the following molecules:

a. 

b. 

c. 

87. a. Draw the two chair conformers for each of the stereoisomers of *trans*-1-*tert*-butyl-3-methylcyclohexane.
    b. For each pair, indicate which conformer is more stable.

88. a. Do the following compounds have any asymmetric carbons?
    1. $CH_2{=}C{=}CH_2$ 2. $CH_3CH{=}C{=}CHCH_3$
    b. Are they chiral? (*Hint:* Make models.)